National Comprehensive Cancer Network®

Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Colon Cancer

NCCN Evidence Blocks™

Version 2.2017 — March 13, 2017

NCCN.org

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NCCN Guidelines Version 2.2017 Panel Members
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NCCN Evidence Blocks™

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† Medical oncology
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
≠ Pathology
‡ Hematology/Hematology oncology
Þ Internal medicine
ф Diagnostic/Interventional radiology
¤ Gastroenterology
¥ Patient advocate
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NCCN Guidelines Panel Disclosures

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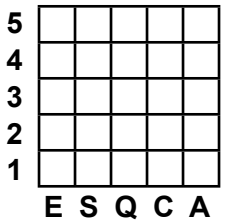
Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

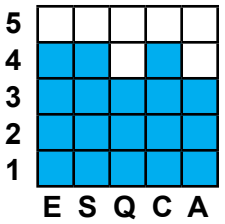
See NCCN Categories of Evidence and Consensus.

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Often provides long-term survival advantage or has curative potential
4	**Very effective:** Sometimes provides long-term survival advantage or has curative potential
3	**Moderately effective:** Modest, no, or unknown impact on survival but often provides control of disease
2	**Minimally effective:** Modest, no, or unknown impact on survival and sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal side effects. No interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only. Little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs is common
2	**Moderately toxic:** Significant toxicities often occur; life threatening/fatal toxicity is uncommon. Interference with ADLs is usual
1	**Highly toxic:** Usually severe, significant toxicities or life threatening/fatal toxicity often observed. Interference with ADLs is usual and/or severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

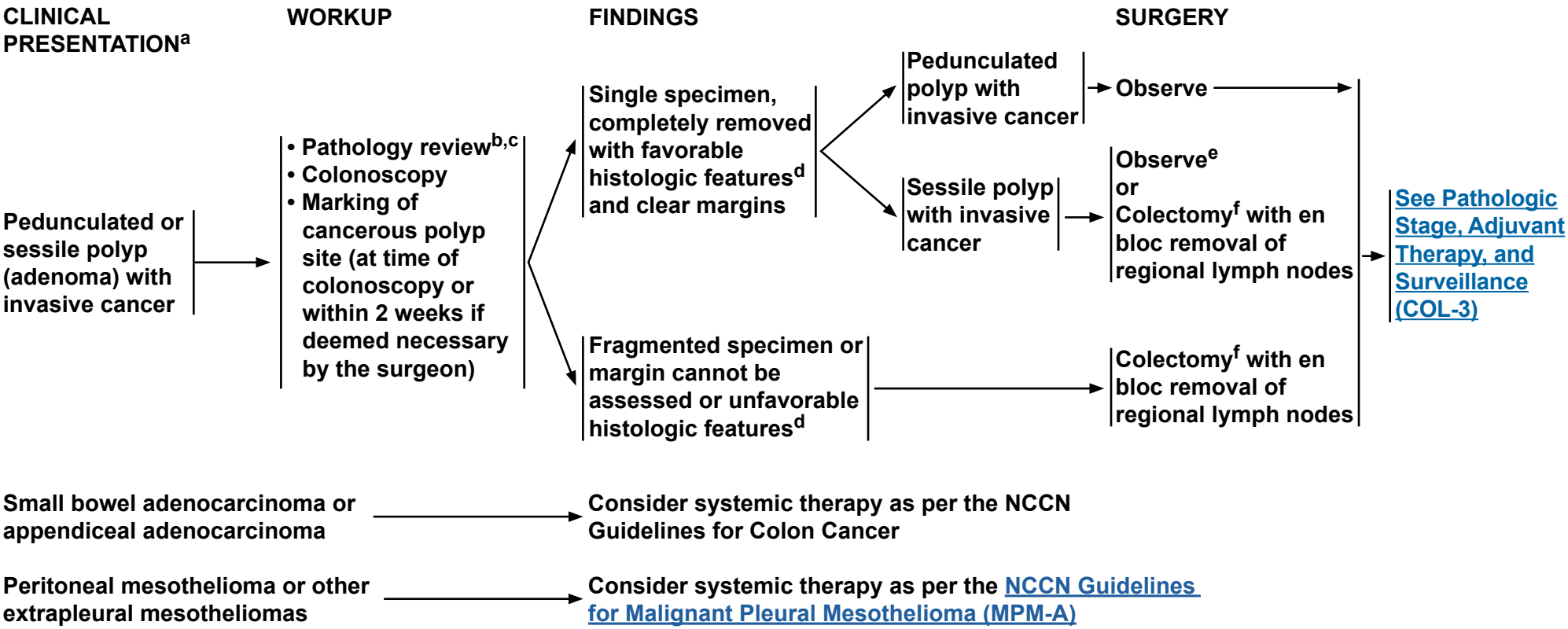
5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** Several well-designed randomized trials
3	**Average quality:** Low quality randomized trials or well-designed non-randomized trials
2	**Low quality:** Case reports or clinical experience only
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients; lower quality trials whether randomized or not
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**



[a]All patients with colon cancer should be counseled for family history and considered for risk assessment. For patients with suspected Lynch syndrome, familial adenomatous polyposis (FAP), and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[b]Confirm the presence of invasive cancer (pT1). pTis has no biological potential to metastasize.
[c]It has not been established if molecular markers are useful in treatment determination (predictive markers) and prognosis. College of American Pathologists Consensus Statement 1999. Prognostic factors in colorectal cancer. Arch Pathol Lab Med 2000;124:979-994.
[d]See Principles of Pathologic Review (COL-A) - Endoscopically removed malignant polyp.
[e]Observation may be considered, with the understanding that there is significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, hematogenous metastasis, but not lymph node metastasis) than polypoid malignant polyps. See Principles of Pathologic Review (COL-A) - Endoscopically removed malignant polyp.
[f]See Principles of Surgery (COL-B 1 of 3).

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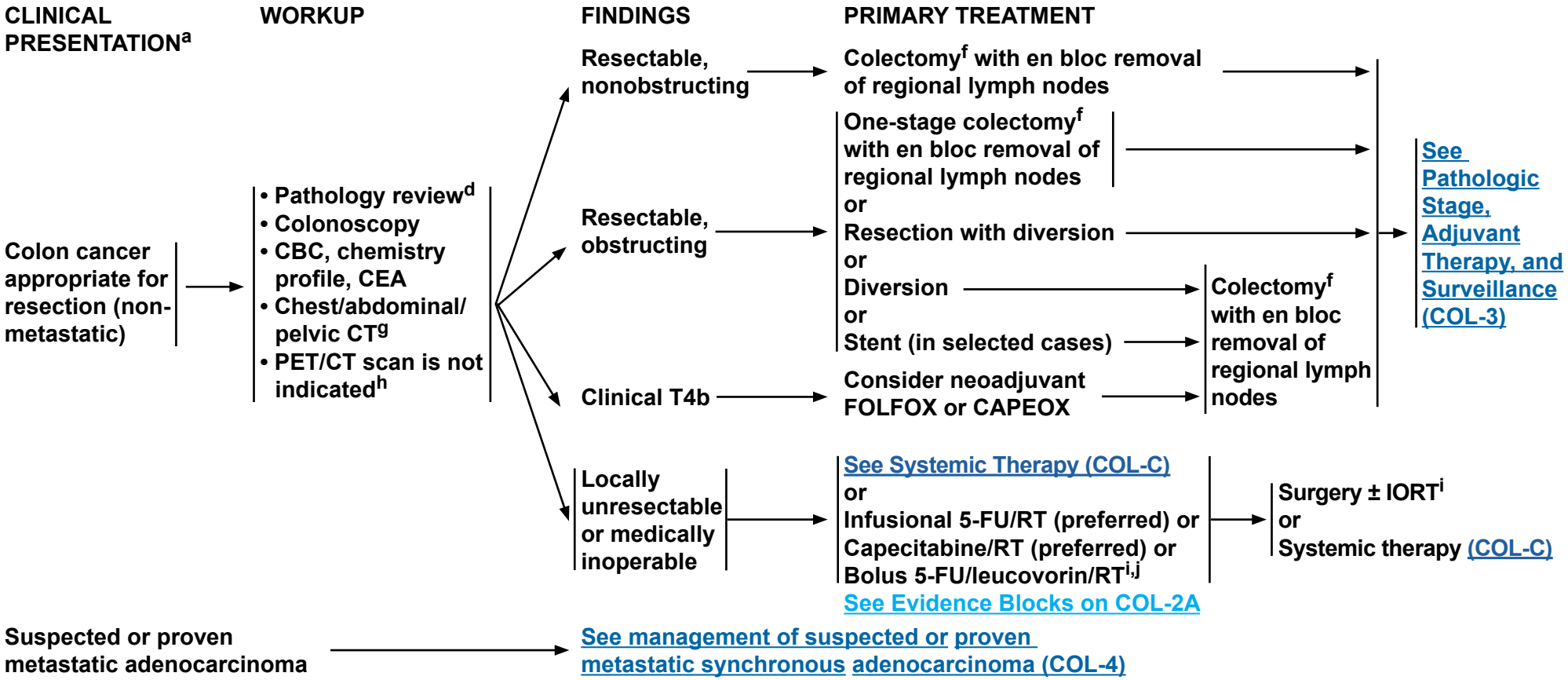

[a]All patients with colon cancer should be counseled for family history and considered for risk assessment. For patients with suspected Lynch syndrome, familial adenomatous polyposis (FAP), and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[d]See Principles of Pathologic Review (COL-A) - Colon cancer appropriate for resection, pathologic stage, and lymph node evaluation.
[f]See Principles of Surgery (COL-B 1 of 3).
[g]CT should be with IV and oral contrast. Consider abdominal/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.
[h]PET/CT does not supplant a contrast-enhanced diagnostic CT scan. PET/CT should only be used to evaluate an equivocal finding on a contrast-enhanced CT scan or in patients with strong contraindications to IV contrast.
[i]See Principles of Radiation Therapy (COL-D).
[j]Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

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EVIDENCE BLOCKS FOR PRIMARY TREATMENT FOR CLINICAL T4b OR LOCALLY UNRESECTABLE OR MEDICALLY INOPERABLE (COL-2)

Bolus 5-FU/leucovorin/RT	
Capecitabine/RT	
Infusional 5-FU/RT	
CapeOx	
FOLFOX	

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PATHOLOGIC STAGE[d]	ADJUVANT TREATMENT
Tis; T1, N0, M0	Observation
T2, N0, M0	Observation
T3, N0, M0[k] (MSI-H or dMMR)	Observation
T3, N0, M0[k] (MSI-L or MSS and no high-risk features)	Clinical trial or Observation or Consider capecitabine[n] or 5-FU/leucovorin[n]
T3, N0, M0 at high risk for systemic recurrence[l,m] or T4, N0, M0	Capecitabine[n,o] or 5-FU/leucovorin[n,o] or FOLFOX[n,o,p,q] or CAPEOX[n,o,p,q] or FLOX[n,o,p,q,r] or Clinical trial or Observation
T any, N1-2, M0	FOLFOX[n,o,q] or CAPEOX[n,o,q] (both category 1 and preferred) Other options include: FLOX (category 1)[n,o,q,r] or Capecitabine[n,o] or 5-FU/leucovorin[n,o]

→ See Surveillance (COL-8)

→ See Evidence Blocks on COL-3A

[d] See Principles of Pathologic Review (COL-A)
[k] See Principles of Risk Assessment for Stage II Disease (COL-E).
[l] High-risk factors for recurrence: poorly differentiated histology (exclusive of those cancers that are MSI-H), lymphatic/vascular invasion, bowel obstruction, <12 lymph nodes examined, perineural invasion, localized perforation, or close, indeterminate, or positive margins. In high-risk stage II patients, there are no data that correlate risk features and selection of chemotherapy.
[m] There are insufficient data to recommend the use of multi-gene assay panels to determine adjuvant therapy.
[n] See Principles of Adjuvant Therapy (COL-F).
[o] Consider RT for T4 with penetration to a fixed structure. See Principles of Radiation Therapy (COL-D).
[p] A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer. Tournigand C, André T, Bonnetain F, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. J Clin Oncol 2012; published online ahead of print on August 20, 2012.
[q] A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.
[r] Grade 3-4 diarrhea is considerably higher with FLOX than FOLFOX in cross-study comparison.

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EVIDENCE BLOCKS FOR ADJUVANT THERAPY
(COL-3)

	Stage II - No high-risk features	Stage II - High-risk features	Stage III
Bolus 5-FU/leucovorin			
Capecitabine			
CapeOx	—		
FLOX	—		
FOLFOX	—		
Infusional 5-FU/leucovorin			

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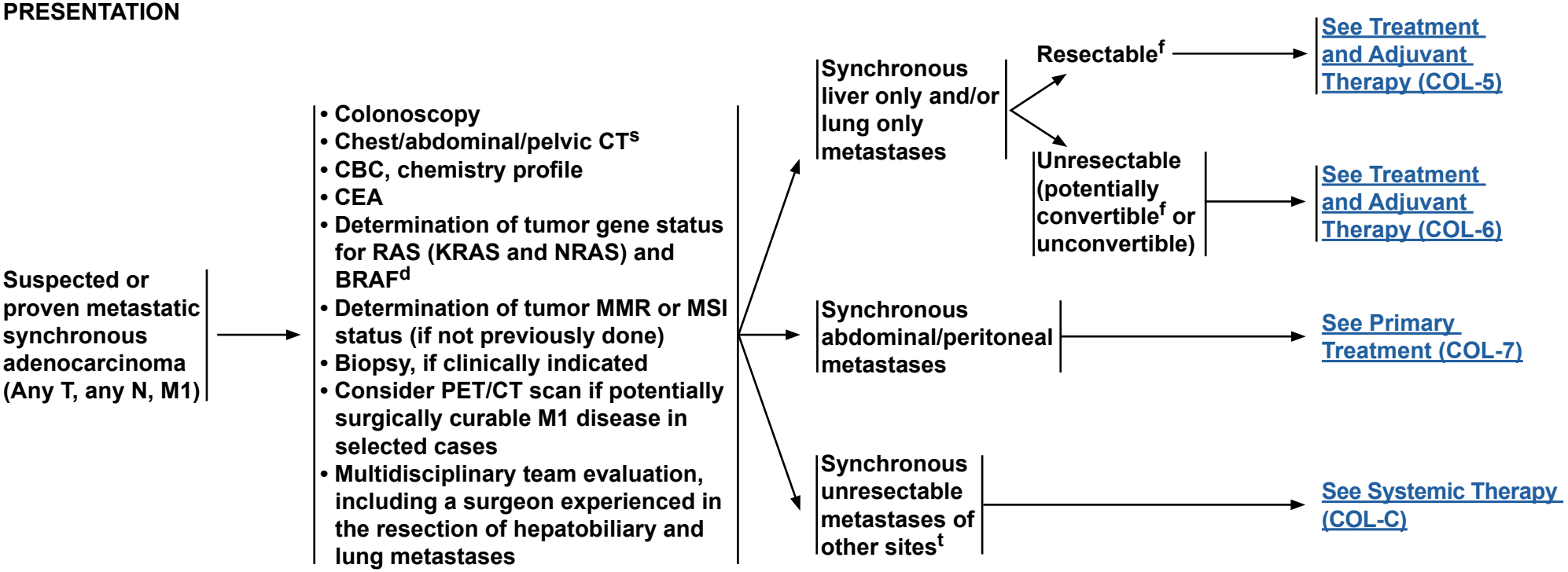

[d] See Principles of Pathologic Review (COL-A 4 of 5) - KRAS, NRAS, and BRAF Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.
[f] See Principles of Surgery (COL-B 2 of 3).
[s] CT should be with IV contrast. Consider MRI with IV contrast if CT is inadequate. PET/CT may be considered for patients who cannot receive contrast.
[t] Consider colon resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.

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TREATMENT
Resectable[f] synchronous liver and/or lung metastases only

ADJUVANT TREATMENT[w]
(resected metastatic disease)

Synchronous or staged colectomy[u] with liver or lung resection (preferred) and/or local therapy[v]
or
Neoadjuvant therapy (for 2–3 months) FOLFOX (preferred) or CAPEOX (preferred) or FOLFIRI (category 2B) followed by synchronous or staged colectomy[u] and resection of metastatic disease
or
Colectomy,[u] followed by chemotherapy (for 2–3 months) FOLFOX (preferred) or CAPEOX (preferred) or FOLFIRI (category 2B) and staged resection of metastatic disease

→

FOLFOX (preferred) or CAPEOX (preferred)
or
FLOX or Capecitabine or 5-FU/leucovorin
(6 MO TOTAL PERIOPERATIVE TREATMENT PREFERRED)

→ See Surveillance (COL-8)

See Evidence Blocks on COL-5A

[f] See Principles of Surgery (COL-B 2 of 3).
[u] Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
[v] Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (COL-B and COL-D).
[w] Imaging (Chest/Abdomen/Pelvic CT with contrast) to be performed prior to adjuvant treatment to assess response to primary therapy or resection.

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EVIDENCE BLOCKS FOR NEOADJUVANT/ADJUVANT THERAPY FOR RESECTABLE SYNCHRONOUS LIVER AND/OR LUNG METASTASES (COL-5)

	Neoadjuvant Therapy or Between Resection	Adjuvant Therapy
5-FU/leucovorin	—	
Capecitabine	—	
CapeOx		
FLOX	—	
FOLFIRI		—
FOLFOX		

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

TREATMENT

Unresectable[f] synchronous liver and/or lung metastases only

- **Systemic therapy (FOLFIRI or FOLFOX or CAPEOX ± bevacizumab[x] or FOLFIRI or FOLFOX ± panitumumab or cetuximab[y] [*KRAS/NRAS* WT gene and left-sided tumors only][d,z,aa] or FOLFOXIRI ± bevacizumab**
- **Consider colon resection[f] only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms**

→ **Re-evaluate for conversion to resectable[f] every 2 mo if conversion to resectability is a reasonable goal**

→ **Converted to resectable** → **Synchronized or staged resection[f] of colon and metastatic cancer**

ADJUVANT TREATMENT[w]

→ **Systemic therapy ± biologic therapy (COL-C) (category 2B for biologic therapy) or Consider observation or shortened course of chemotherapy (6 MO TOTAL PERIOPERATIVE TREATMENT PREFERRED)**

→ **See Surveillance (COL-8)**

→ **Remains unresectable** → **See Systemic Therapy (COL-C)**

See Evidence Blocks on COL-C (EB-1)

See Recurrence (COL-9)

[d] See Principles of Pathologic Review (COL-A 4 of 5) - *KRAS, NRAS,* and *BRAF* Mutation Testing.
[f] See Principles of Surgery (COL-B 2 of 3).
[w] Imaging (Chest/Abdomen/Pelvic CT with contrast) to be performed prior to adjuvant treatment to assess response to primary therapy or resection.
[x] There should be at least a 6-week interval between the last dose of bevacizumab and elective surgery and re-initiation of bevacizumab at least 6–8 weeks postoperatively. There is an increased risk of stroke and other arterial events, especially in those aged ≥65 years. The use of bevacizumab may interfere with wound healing.
[y] There are conflicting data regarding the use of FOLFOX + cetuximab in patients who have potentially resectable liver metastases.
[z] BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely.
[aa] The panel defines the left side of the colon as splenic flexure to rectum. Evidence suggests that patients with tumors originating on the right side of the colon (hepatic flexure through cecum) are unlikely to respond to cetuximab and panitumumab in first-line therapy for metastatic disease. Data on the response to cetuximab and panitumumab in patients with primary tumors originating in the transverse colon (hepatic flexure to splenic flexure) are lacking.

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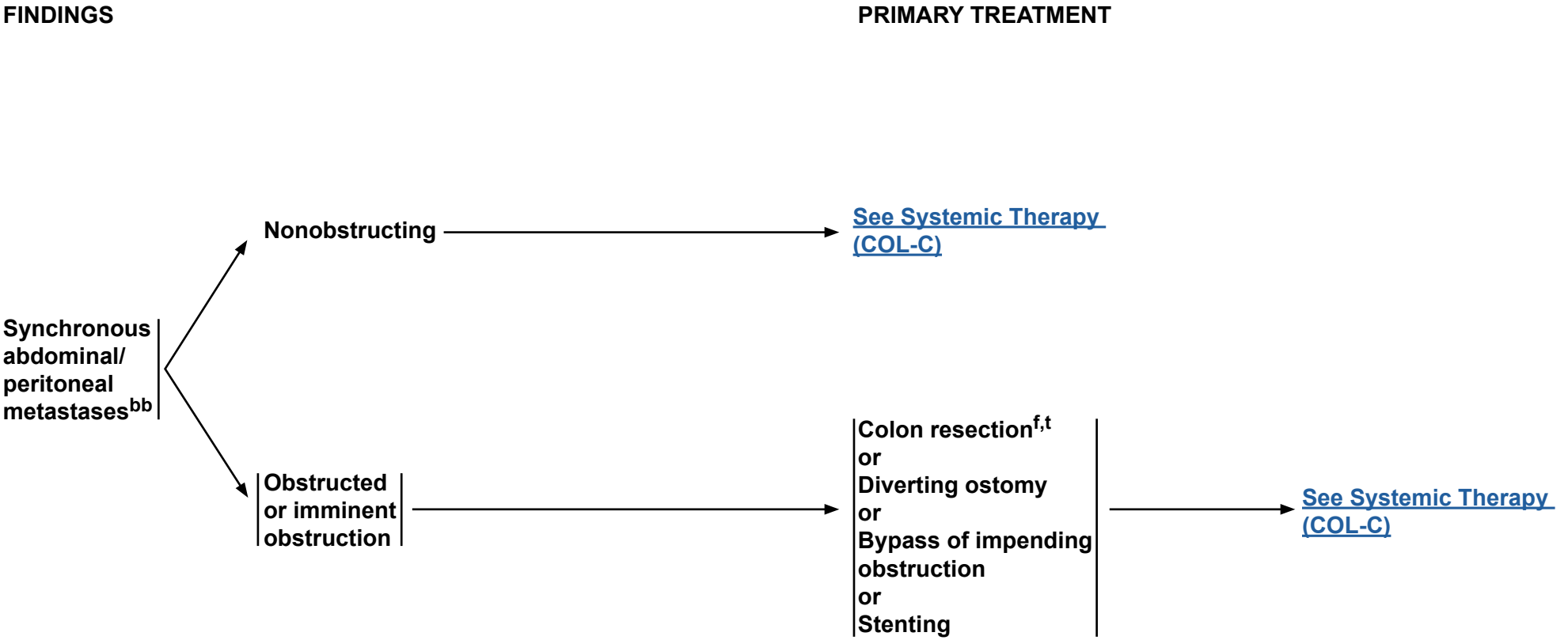

[f] See Principles of Surgery (COL-B 2 of 3).
[t] Consider colon resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.
[bb] Complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for select patients with limited peritoneal metastases for whom R0 resection can be achieved.

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PATHOLOGIC STAGE	SURVEILLANCE
Stage I	Colonoscopy at 1 y ▸ If advanced adenoma, repeat in 1 y ▸ If no advanced adenoma,[cc] repeat in 3 y, then every 5 y[dd]
Stage II, III	• History and physical every 3–6 mo for 2 y, then every 6 mo for a total of 5 y • CEA[ee] every 3–6 mo for 2 y, then every 6 mo for a total of 5 y • Chest/abdominal/pelvic CT[g] every 6–12 mo (category 2B for frequency <12 mo) for a total of 5 y • Colonoscopy[a] in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3–6 mo ▸ If advanced adenoma, repeat in 1 y ▸ If no advanced adenoma,[cc] repeat in 3 y, then every 5 y[dd] • PET/CT scan is not recommended • See Principles of Survivorship (COL-G)
Stage IV	• History and physical every 3–6 mo for 2 y, then every 6 mo for a total of 5 y • CEA every 3–6 mo x 2 y, then every 6 mo x 3–5 y • Chest/abdominal/pelvic CT[g] scan every 3–6 mo (category 2B for frequency <6 mo) x 2 y, then every 6–12 mo for a total of 5 y • Colonoscopy[a] in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3–6 mo ▸ If advanced adenoma, repeat in 1 y ▸ If no advanced adenoma,[cc] repeat in 3 y, then every 5 y[dd] • See Principles of Survivorship (COL-G)

Serial CEA elevation or documented recurrence → See Workup and Treatment (COL-9)

[a]All patients with colon cancer should be counseled for family history and considered for risk assessment. For patients with suspected Lynch syndrome, familial adenomatous polyposis (FAP), and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[g]CT should be with IV and oral contrast. Consider abdominal/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.
[cc]Villous polyp, polyp >1 cm, or high-grade dysplasia.
[dd]Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2006;130:1865-71.
[ee]If patient is a potential candidate for further intervention.

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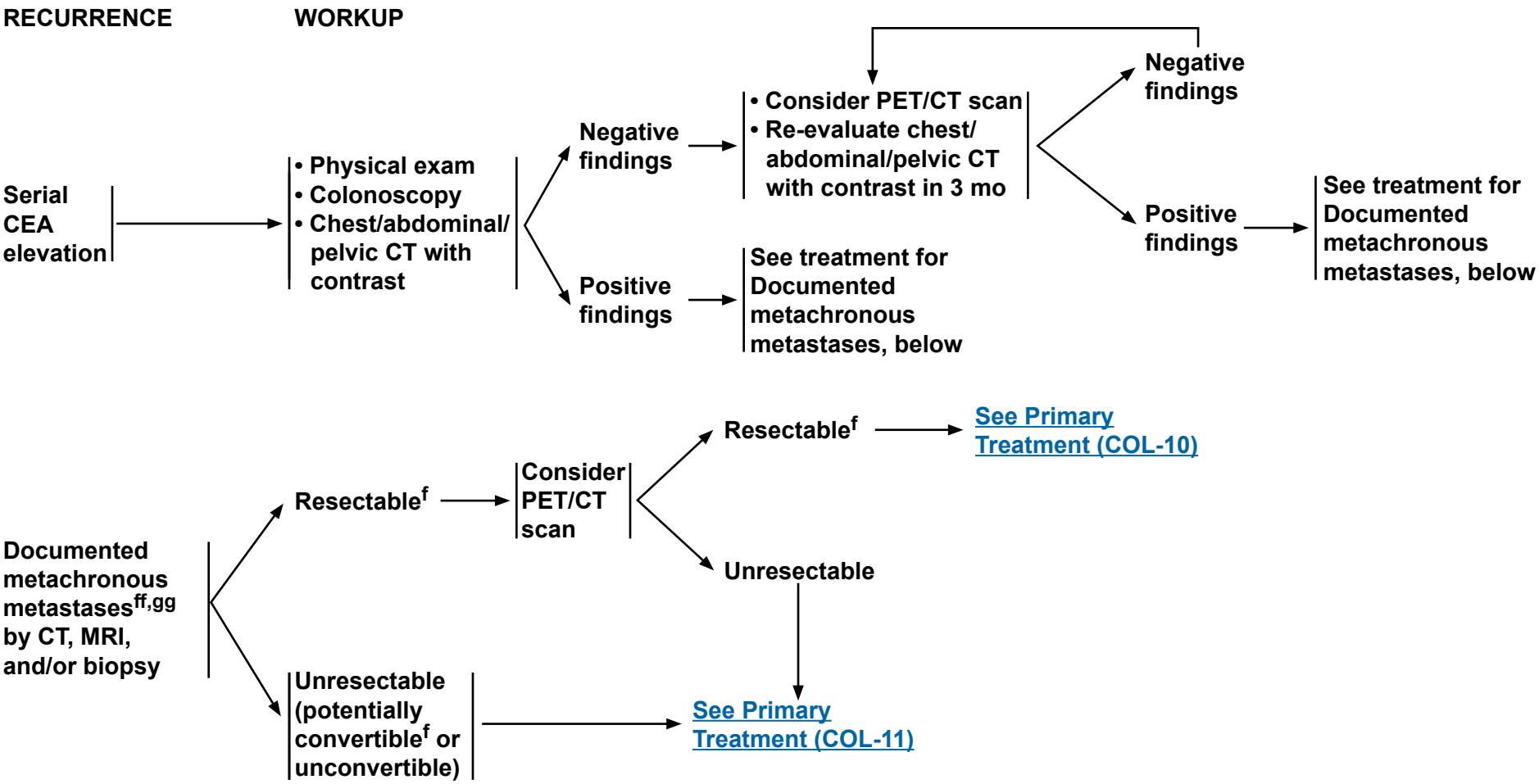

[f] See Principles of Surgery (COL-B 2 of 3).
[ff] Determination of tumor gene status for RAS (KRAS and NRAS) and BRAF. Determination of tumor MMR or MSI status (if not previously done). See Principles of Pathologic Review (COL-A 4 of 5) - *KRAS*, *NRAS* and *BRAF* Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.
[gg] Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.

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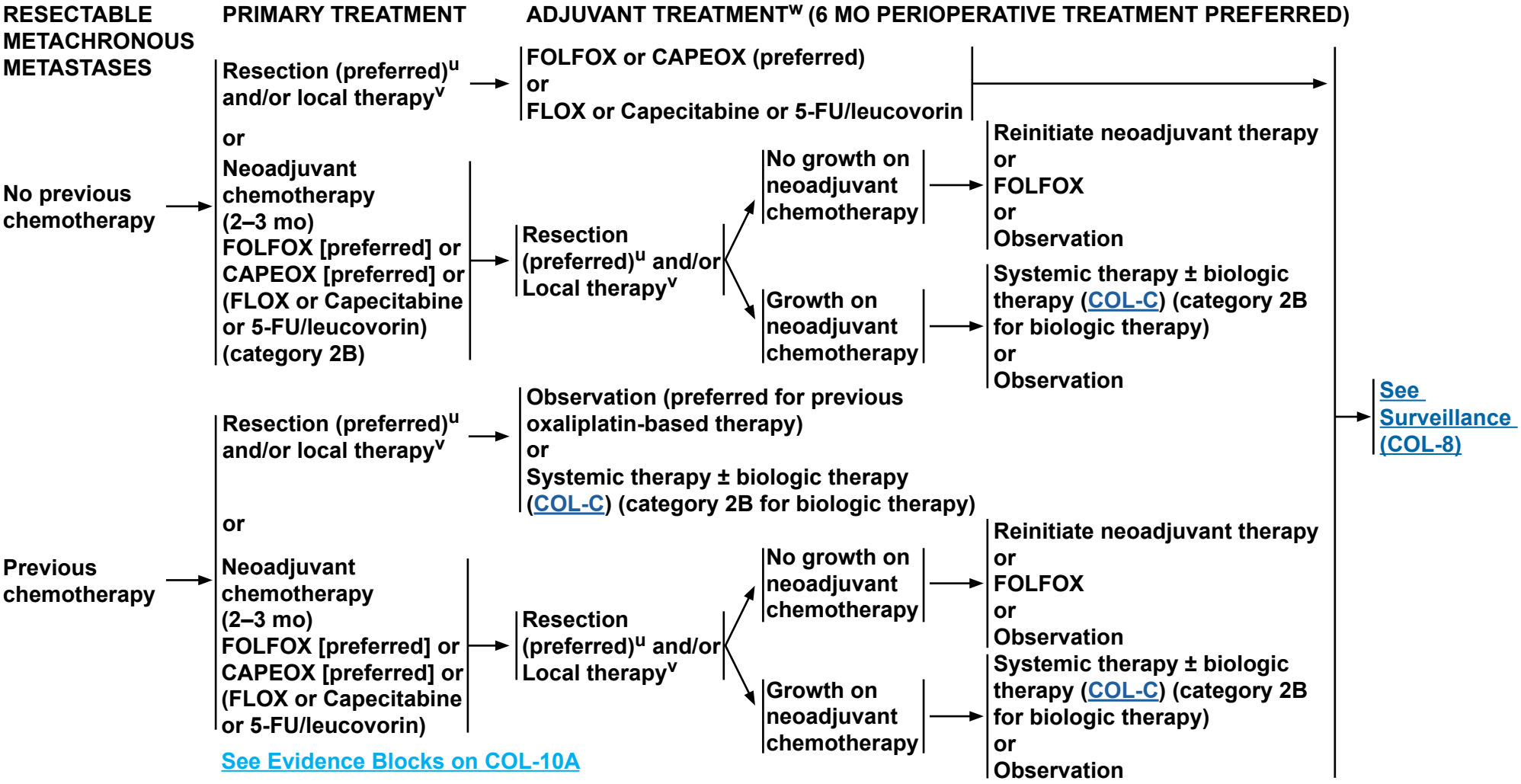

[u]Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
[v]Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (COL-B and COL-D).
[w]Imaging (Chest/Abdomen/Pelvic CT with contrast) to be performed prior to adjuvant treatment to assess response to primary therapy or resection.

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EVIDENCE BLOCKS FOR NEOADJUVANT/ADJUVANT THERAPY FOR RESECTABLE METACHRONOUS METASTASES (COL-10)

	Neoadjuvant Therapy (with or without previous chemotherapy)	Adjuvant Therapy
5-FU/leucovorin		
Capecitabine		
CapeOx		
FLOX		
FOLFOX		

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UNRESECTABLE METACHRONOUS METASTASES

PRIMARY TREATMENT

- **Previous adjuvant FOLFOX/CAPEOX within past 12 months** →
  - **FOLFIRI ± (bevacizumab [preferred] or ziv-aflibercept or ramucirumab)[hh]**
  - **or**
  - **Irinotecan ± (bevacizumab [preferred] or ziv-aflibercept or ramucirumab)[hh]**
  - **or**
  - **FOLFIRI + (cetuximab or panitumumab) (*KRAS/NRAS* WT gene only)[d,z]**
  - **or**
  - **Irinotecan ± (Cetuximab or panitumumab) (*KRAS/NRAS* WT gene only)[d,z]**
  - **or**
  - **(Nivolumab or pembrolizumab) (dMMR/MSI-H only)**
- **Previous adjuvant FOLFOX/CAPEOX >12 months**
- **Previous 5-FU/LV or capecitabine**
- **No previous chemotherapy** →
  - **Systemic therapy (COL-C)**

→ **Re-evaluate for conversion to resectable[f] every 2 mo if conversion to resectability is a reasonable goal**

- **Converted to resectable** → **Resection[u]** → **Systemic therapy ± biologic therapy (COL-C) (category 2B for biologic therapy) or Observation** → **See Surveillance (COL-8)**
- **Remains unresectable** → **Systemic therapy (COL-C)**

ADJUVANT TREATMENT[w] (6 MO PERIOPERATIVE TREATMENT PREFERRED)

See Evidence Blocks on COL-C (EB-2)

[d] See Principles of Pathologic Review (COL-A 4 of 5) - *KRAS, NRAS,* and *BRAF* Mutation Testing.
[f] See Principles of Surgery (COL-B 2 of 3).
[u] Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
[w] Imaging (Chest/Abdomen/Pelvic CT with contrast) to be performed prior to adjuvant treatment to assess response to primary therapy or resection.
[z] BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely.
[hh] Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.

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PRINCIPLES OF PATHOLOGIC REVIEW (1 of 5)

Endoscopically Removed Malignant Polyps

- A malignant polyp is defined as one with cancer invading through the muscularis mucosa and into the submucosa (pT1). pTis is not considered a "malignant polyp."
- Favorable histologic features: grade 1 or 2, no angiolymphatic invasion, and negative margin of resection. There is no consensus as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as 1) tumor <1 mm from the transected margin; 2) tumor <2 mm from the transected margin; and 3) tumor cells present within the diathermy of the transected margin.[1-4]
- Unfavorable histologic features: grade 3 or 4, angiolymphatic invasion, or a "positive margin." See the positive margin definition above. In several studies, tumor budding has been shown to be an adverse histological feature associated with adverse outcome and may preclude polypectomy as an adequate treatment of endoscopically removed malignant polyps.
- There is controversy as to whether malignant colorectal polyps with a sessile configuration can be successfully treated by endoscopic removal. The literature seems to indicate that endoscopically removed sessile malignant polyps have a significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, and hematogenous metastasis, but not lymph node metastasis) than do pedunculated malignant polyps. However, when one closely looks at the data, configuration by itself is not a significant variable for adverse outcome, and endoscopically removed malignant sessile polyps with grade I or II histology, negative margins, and no lymphovascular invasion can be successfully treated with endoscopic polypectomy.[3-7]

Colon Cancer Appropriate for Resection

- Histologic confirmation of primary colonic malignant neoplasm.

Pathologic Stage

- The following parameters should be reported:
  - Grade of the cancer
  - Depth of penetration (T)
  - Number of lymph nodes evaluated and number positive (N)
  - Status of proximal, distal, radial, and mesenteric margins[8-9] See Staging (ST-1)
  - Lymphovascular invasion[10,11]
  - Perineural invasion (PNI)[12-14]
  - Tumor deposits[15-18]

See Pathologic Stage (continued) on COL-A 2 of 5

See Lymph Node Evaluation on COL-A 3 of 5

See KRAS, NRAS, and BRAF Mutation Testing on COL-A 4 of 5

See references on COL-A 5 of 5

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PRINCIPLES OF PATHOLOGIC REVIEW (2 of 5)

Pathologic Stage (continued)

- **Radial (circumferential) margin evaluation - The serosal surface (peritoneal) does not constitute a surgical margin. In colon cancer the circumferential (radial) margin represents the adventitial soft tissue closest to the deepest penetration of tumor, and is created surgically by blunt or sharp dissection of the retroperitoneal aspect. The radial margins should be assessed in all colonic segments with non-peritonealized surfaces. The circumferential resection margin corresponds to any aspect of the colon that is not covered by a serosal layer of mesothelial cells, and must be dissected from the retroperitoneum to remove the viscus. On pathologic examination it is difficult to appreciate the demarcation between a peritonealized surface and non-peritonealized surface. Therefore, the surgeon is encouraged to mark the area of non-peritonealized surface with a clip or suture. The mesenteric resection margin is the only relevant circumferential margin in segments completely encased by the peritoneum.[10-11]**
- **PNI - The presence of PNI is associated with a significantly worse prognosis. In multivariate analysis, PNI has been shown to be an independent prognostic factor for cancer-specific, overall, and disease-free survival. For stage II carcinoma, those with PNI have a significantly worse 5-year disease-free survival compared to those without PNI (29% vs. 82% [*P* = .0005]).[12-14]**
- **Tumor deposits - Irregular discrete tumor deposits in pericolic or perirectal fat away from the leading edge of the tumor and showing no evidence of residual lymph node tissue, but within the lymphatic drainage of the primary carcinoma, are considered peritumoral deposits or satellite nodules and are not counted as lymph nodes replaced by tumor. Most examples are due to lymphovascular or, more rarely, PNI. Because these tumor deposits are associated with reduced disease-free and overall survival, their number should be recorded in the surgical pathology report. This poorer outcome has also been noted in patients with stage III carcinoma.[15-18]**

See Endoscopically Removed Malignant Polyps and Colon Cancer Appropriate for Resection on COL-A 1 of 5
See Lymph Node Evaluation on COL-A 3 of 5
See KRAS, NRAS, and BRAF Mutation Testing on COL-A 4 of 5
See references on COL-A 5 of 5

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PRINCIPLES OF PATHOLOGIC REVIEW (3 of 5)

Lymph Node Evaluation

- The AJCC and College of American Pathologists recommend examination of a minimum of 12 lymph nodes to accurately stage colon cancers.[8,9,19] The literature lacks consensus as to what is the minimal number of lymph nodes to accurately identify stage II cancer. The minimal number of nodes has been reported as >7, >9, >13, >20, and >30.[20-28] The number of lymph nodes retrieved can vary with age of the patient, gender, tumor grade, and tumor site.[21] For stage II (pN0) colon cancer, if fewer than 12 lymph nodes are initially identified, it is recommended that the pathologist go back to the specimen and resubmit more tissue of potential lymph nodes. If 12 lymph nodes are still not identified, a comment in the report should indicate that an extensive search for lymph nodes was undertaken. The pathologist should attempt to retrieve as many lymph nodes as possible. It has been shown that the number of negative lymph nodes is an independent prognostic factor for patients with stage IIIB and IIIC colon cancer.[29]

Sentinel Lymph Node and Detection of Micrometastasis by Immunohistochemistry

- Examination of the sentinel lymph node allows an intense histologic and/or immunohistochemical investigation to detect the presence of metastatic carcinoma. Studies in the literature have been reported using multiple hematoxylin and eosin (H&E) sections and/or immunohistochemistry (IHC) to detect cytokeratin-positive cells.[30-34] The significance of detection of single cells by IHC alone is controversial. The 7th edition of the AJCC Cancer Staging Manual and Handbook[35] considers “tumor clusters” <0.2 mm to be isolated tumor cells (pN0) and not metastatic carcinoma. However, some investigators believe that size should not affect the diagnosis of metastatic cancer. They believe that tumor foci that show evidence of growth (eg, glandular differentiation, distension of sinus, stromal reaction) should be diagnosed as a lymph node metastasis regardless of size.[36]
- Some studies have shown that the detection of IHC cytokeratin-positive cells in stage II (N0) colon cancer (defined by H&E) has a worse prognosis, while others have failed to show this survival difference. In these studies, isolated tumor cells were considered to be micrometastases.[37-42]
- At the present time the use of sentinel lymph nodes and detection of cancer cells by IHC alone should be considered investigational, and results should be used with caution in clinical management decisions.[30-34,38-42]

See Endoscopically Removed Malignant Polyp and Colon Cancer Appropriate for Resection on COL-A 1 of 5

See Pathologic Stage on COL-A 2 of 5

See KRAS, NRAS, and BRAF Mutation Testing on COL-A 4 of 5

See references on COL-A 5 of 5

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PRINCIPLES OF PATHOLOGIC REVIEW (4 of 5)

***KRAS*, *NRAS*, and *BRAF* Mutation Testing**

- **All patients with metastatic colorectal cancer should have tumor tissue genotyped for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations. Patients with any known *KRAS* mutation (exon 2 or non-exon 2) or *NRAS* mutation should not be treated with either cetuximab or panitumumab.[43,44,45] *BRAF V600E* mutation makes response to panitumumab or cetuximab highly unlikely.[46-48]**
- **Testing for *KRAS*, *NRAS*, and *BRAF* mutations should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform *high complexity* clinical laboratory (molecular pathology) testing. No specific methodology is recommended (eg, sequencing, hybridization).**
- **The testing can be performed on formalin-fixed paraffin-embedded tissue. The testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the *KRAS*, *NRAS*, and *BRAF* mutations are similar in both specimen types.[49]**

Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing

- **Universal MMR* or MSI* testing is recommended in all patients with a personal history of colon or rectal cancer. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal**
- **The presence of a BRAF V600E mutation in the setting of MLH1 absence would preclude the diagnosis of Lynch syndrome.**
- **Stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy.[50]**
- **MMR or MSI testing should be performed only in CLIA-approved laboratories.**

*IHC for MMR and PCR for MSI are different assays measuring the same biological effect.

See Endoscopically Removed Malignant Polyps and Colon Cancer Appropriate for Resection on COL-A 1 of 5

See Pathologic Stage on COL-A 2 of 5

See Lymph Node Evaluation on COL-A 3 of 5

See references on COL-A 5 of 5

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PRINCIPLES OF PATHOLOGIC REVIEW - References (5 of 5)

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PRINCIPLES OF SURGERY (1 of 3)

Colectomy

- **Lymphadenectomy**
  - **Lymph nodes at the origin of feeding vessel(s) should be identified for pathologic exam.**
  - **Clinically positive lymph nodes outside the field of resection that are considered suspicious should be biopsied or removed, if possible.**
  - **Positive nodes left behind indicate an incomplete (R2) resection.**
  - **A minimum of 12 lymph nodes need to be examined to establish N stage.[1]**
- **Minimally invasive approaches may be considered based on the following criteria:[2]**
  - **The surgeon has experience performing laparoscopically assisted colorectal operations.[3,4]**
  - **There is no locally advanced disease.**
  - **It is not indicated for acute bowel obstruction or perforation from cancer.**
  - **Thorough abdominal exploration is required.[5]**
  - **Consider preoperative marking of lesion(s).**
- **Management of patients with carrier status of known or clinically suspected Lynch syndrome**
  - **Consider more extensive colectomy for patients with a strong family history of colon cancer or young age (<50 y).**

  See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
- **Resection needs to be complete to be considered curative.**

See Criteria for Resectability of Metastases and Locoregional Therapies Within Surgery on COL-B 2 of 3

See footnotes on COL-B 3 of 3

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PRINCIPLES OF SURGERY (2 of 3)
CRITERIA FOR RESECTABILITY OF METASTASES AND LOCOREGIONAL THERAPIES WITHIN SURGERY

Liver

- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.[6]
- Complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of adequate hepatic function is required.[7]
- The primary tumor must have been resected for cure (R0). There should be no unresectable extrahepatic sites of disease.[8-11] Having a plan for a debulking resection (less than an R0 resection) is not recommended.[7]
- Patients with resectable metastatic disease and a primary tumor in place should have both sites resected with curative intent. These can be resected in one operation or as a staged approach, depending on the complexity of the hepatectomy or colectomy, comorbid diseases, surgical exposure, and surgeon expertise.[12]
- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches utilizing preoperative portal vein embolization[13] or staged liver resection[14] can be considered.
- Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection.
- Arterially directed catheter therapy, and in particular yttrium 90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable.
- Re-resection can be considered in selected patients.[15]

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.[16-19]
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.[20-23]
- Re-resection can be considered in selected patients.[24]
- Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection.
- Ablative techniques can be considered when unresectable and amenable to complete ablation.
- Patients with resectable synchronous metastases can be resected synchronously or using a staged approach.
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable.

Evaluation for Conversion to Resectable Disease

- Re-evaluation for resection should be considered in otherwise unresectable patients after 2 months of preoperative chemotherapy and every 2 months thereafter.[25-28]
- Disease with a higher likelihood of being converted to resectable are those with initially convertible disease distributed within limited sites.
- When considering whether disease has been converted to resectable, all original sites need to be amenable to resection.[29]
- Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.[30]

See footnotes on COL-B 3 of 3

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PRINCIPLES OF SURGERY - REFERENCES (3 of 3)

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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 1 of 10)

Patient appropriate for intensive therapy[2]

Initial Therapy

- **FOLFOX ± bevacizumab**
  or
  CAPEOX ± bevacizumab
  or
  FOLFOX + (cetuximab or panitumumab)[3-5]
  (KRAS/NRAS WT and left-sided tumors only)
  → **Progression** → See COL-C 2 of 10
- **or**
  FOLFIRI[6] ± bevacizumab
  or
  FOLFIRI[6] + (cetuximab or panitumumab)[3-5]
  (KRAS/NRAS WT and left-sided tumors only)
  → **Progression** → See COL-C 3 of 10
- **or**
  FOLFOXIRI[6] ± bevacizumab
  → **Progression** → See COL-C 4 of 10
- **or**
  5-FU/leucovorin (infusional preferred) ± bevacizumab[7]
  or
  Capecitabine ± bevacizumab[7]
  → **Progression** → See COL-C 5 of 10

See Evidence Blocks on COL-C (EB-1)

Patient not appropriate for intensive therapy[2]

- **Infusional 5-FU + leucovorin ± bevacizumab**
  or
  Capecitabine ± bevacizumab
  or
  (Cetuximab or panitumumab)[3-5]
  (category 2B) (KRAS/NRAS WT and left-sided tumors only
  or
  (Nivolumab or pembrolizumab)
  (dMMR/MSI-H only)[3]

  → **Improvement in functional status** → **Consider initial therapy as above[8]**

  → **No improvement in functional status** → **Best supportive care**
  See NCCN Guidelines for Palliative Care

See footnotes COL-C 6 of 10

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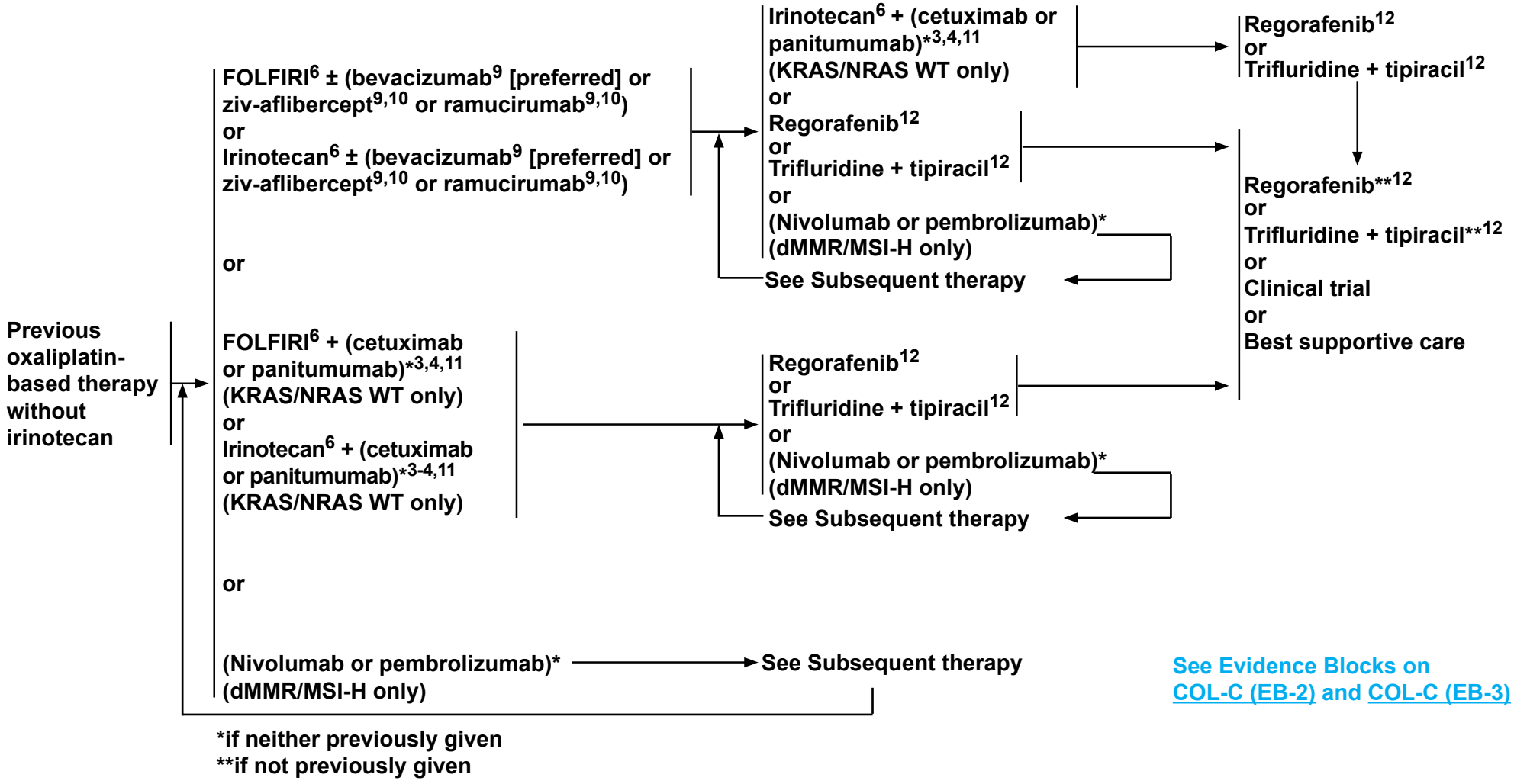
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 2 of 10)

Subsequent Therapy



*if neither previously given
**if not previously given

See Evidence Blocks on COL-C (EB-2) and COL-C (EB-3)

See footnotes COL-C 6 of 10

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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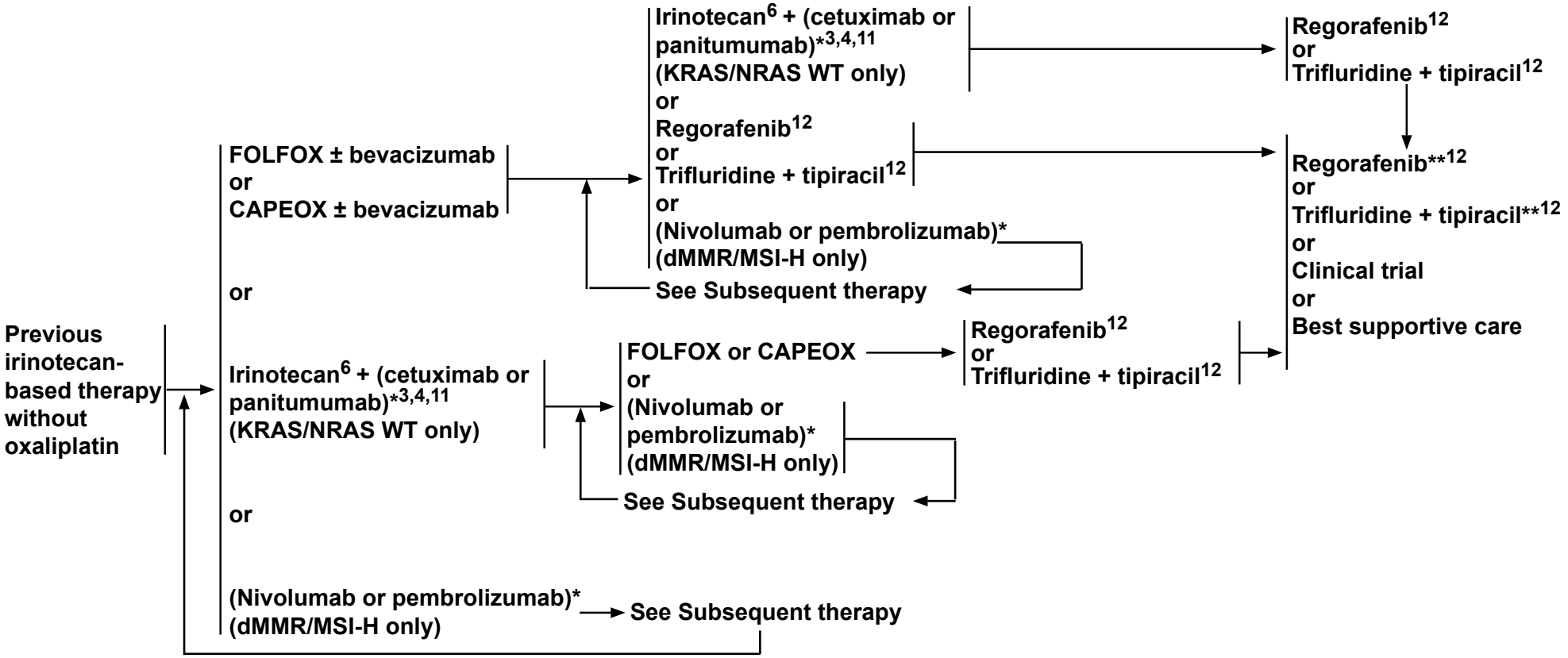
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 3 of 10)

Subsequent Therapy



*if neither previously given
**if not previously given

See Evidence Blocks on COL-C (EB-2) and COL-C (EB-3)

See footnotes COL-C 6 of 10

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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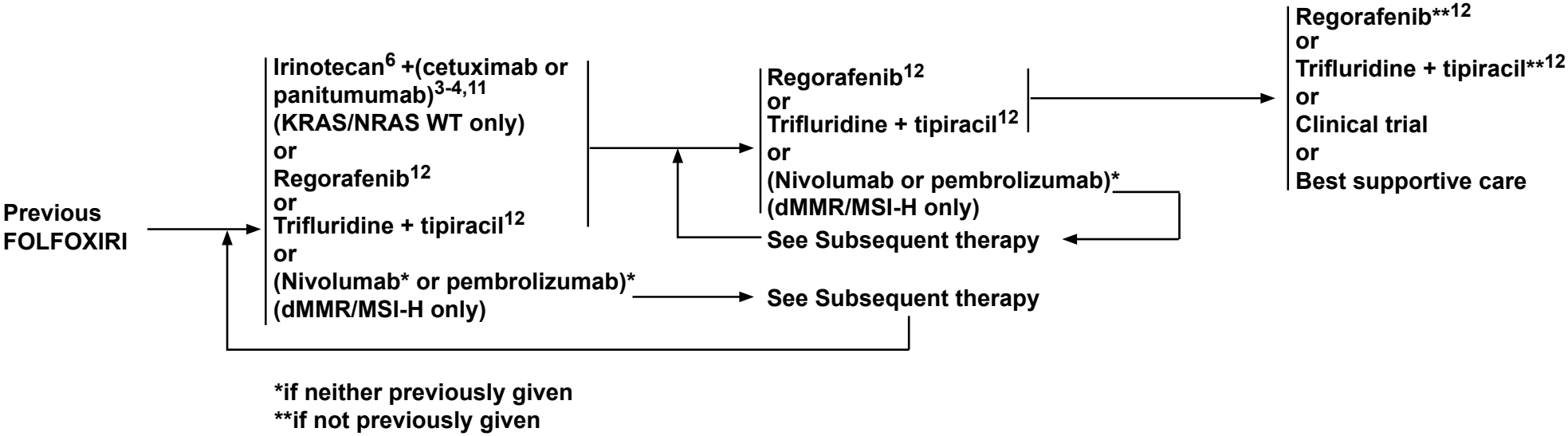
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 4 of 10)

Subsequent Therapy



*if neither previously given
**if not previously given

See Evidence Blocks on COL-C (EB-2) and COL-C (EB-3)

See footnotes COL-C 6 of 10

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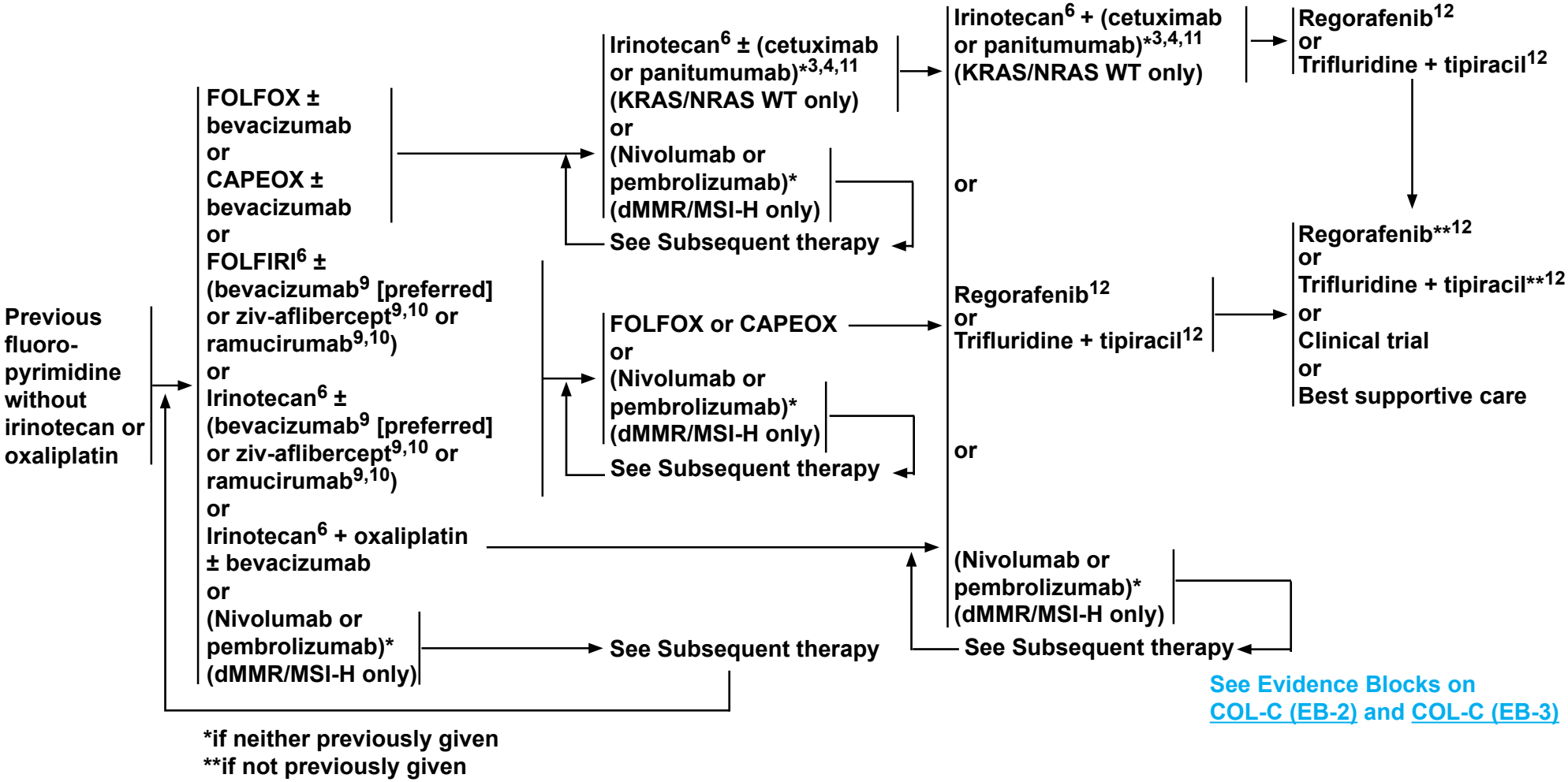
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 5 of 10)

Subsequent Therapy



*if neither previously given
**if not previously given

See Evidence Blocks on COL-C (EB-2) and COL-C (EB-3)

See footnotes COL-C 6 of 10

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EVIDENCE BLOCKS FOR ADVANCED OR METASTATIC DISEASE
COL-C (1 of 10)

Regimen	First-Line Therapy
5-FU/leocovorin	
5-FU/leucovorin + bevacizumab	
Capecitabine	
Capecitabine + bevacizumab	
CapeOx	
CapeOx + bevacizumab	
Cetuximab	
FOLFIRI	
FOLFIRI + bevacizumab	
FOLFIRI + cetuximab	
FOLFIRI + panitumumab	

Regimen	First-Line Therapy
FOLFOX	
FOLFOX + bevacizumab	
FOLFOX + cetuximab	
FOLFOX + panitumumab	
FOLFOXIRI	
FOLFOXIRI + bevacizumab	
Nivolumab	
Panitumumab	
Pembrolizumab	

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EVIDENCE BLOCKS FOR ADVANCED OR METASTATIC DISEASE

Regimen	Second-Line Therapy
CapeOx	
CapeOx + bevacizumab (after prior bevacizumab)	
CapeOx + bevacizumab (no prior bevacizumab)	
Cetuximab	
FOLFIRI	
FOLFIRI + bevacizumab (after prior bevacizumab)	
FOLFIRI + bevacizumab (no prior bevacizumab)	
FOLFIRI + cetuximab	
FOLFIRI + panitumumab	
FOLFIRI + ramucirumab (after prior bevacizumab)	
FOLFIRI + ramucirumab (no prior bevacizumab)	
FOLFIRI + ziv-aflibercept (after prior bevacizumab)	
FOLFIRI + ziv-aflibercept (no prior bevacizumab)	

Regimen	Second-Line Therapy
FOLFOX	
FOLFOX + bevacizumab (after prior bevacizumab)	
FOLFOX + bevacizumab (no prior bevacizumab)	
Irinotecan	
Irinotecan + bevacizumab (after prior bevacizumab)	
Irinotecan + bevacizumab (no prior bevacizumab)	
Irinotecan + cetuximab	
Irinotecan + oxaliplatin	
IROX + bevacizumab (after prior bevacizumab)	
IROX + bevacizumab (no prior bevacizumab)	

Regimen	Second-Line Therapy
Irinotecan + panitumumab	
Irinotecan + ramucirumab (after prior bevacizumab)	
Irinotecan + ramucirumab (no prior bevacizumab)	
Irinotecan + ziv-aflibercept (after prior bevacizumab)	
Irinotecan + ziv-aflibercept (no prior bevacizumab)	
Nivolumab	
Panitumumab	
Pembrolizumab	
Regorafenib	
Trifluridine + tipiracil	

Previous oxaliplatin-based therapy on COL-C (2 of 10)
Previous irinotecan-based therapy on COL-C (3 of 10)
Previous FOLFOXIRI on COL-C (4 of 10)
Previous fluoropyrimidine on COL-C (5 of 10)

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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EVIDENCE BLOCKS FOR ADVANCED OR METASTATIC DISEASE

Regimen	Third-Line Therapy	Subsequent Therapy
CapeOx		
Cetuximab		
FOLFOX		
Irinotecan		—
Irinotecan + cetuximab		
Irinotecan + panitumumab		
Nivolumab		—
Panitumumab		
Pembrolizumab		—
Regorafenib (previous trifluridine + tipiracil)		
Regorafenib (no previous trifluridine + tipiracil)		
Trifluridine + tipiracil (previous regorafenib)		
Trifluridine + tipiracil (no previous regorafenib)		

Previous oxaliplatin-based therapy on COL-C (2 of 10)

Previous irinotecan-based therapy on COL-C (3 of 10)

Previous FOLFOXIRI on COL-C (4 of 10)

Previous fluoropyrimidine on COL-C (5 of 10)

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 6 of 10)

[1]For chemotherapy references, see Chemotherapy Regimens and References (COL-C 7-10).
[2]Chest/Abdominal/Pelvic CT with contrast or Chest CT and Abdominal/Pelvic MRI with contrast to monitor progress of therapy. PET/CT should not be used.
[3]See Principles of Pathologic Review (COL-A 4 of 5).
[4]BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely.
[5]The panel defines the left side of the colon as splenic flexure to rectum. Evidence suggests that patients with tumors originating on the right side of the colon (hepatic flexure through cecum) are unlikely to respond to cetuximab and panitumumab in first-line therapy for metastatic disease. Data on the response to cetuximab and panitumumab in patients with primary tumors originating in the transverse colon (hepatic flexure to splenic flexure) are lacking.
[6]Irinotecan should be used with caution in patients with Gilbert's disease or elevated serum bilirubin. There is a commercially available test for UGT1A1. Guidelines for use in clinical practice have not been established.
[7]A treatment option for patients not able to tolerate oxaliplatin or irinotecan.
[8]The use of single-agent capecitabine after progression on a fluoropyrimidine-containing regimen has been shown to be ineffective; therefore, this is not recommended.
[9]Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.
[10]There are no data to suggest activity of FOLFIRI-ziv-aflibercept or FOLFIRI-ramucirumab in a patient who has progressed on FOLFIRI-bevacizumab, or vice versa. Ziv-aflibercept and ramucirumab have only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients.
[11]Cetuximab or panitumumab are recommended in combination with irinotecan-based therapy or as single-agent therapy for patients who cannot tolerate irinotecan.
[12]Regorafenib or trifluridine + tipiracil are treatment options for patients who have progressed through all available regimens.

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 7 of 10)

mFOLFOX 6[1,2,3]¶
Oxaliplatin 85 mg/m² IV day 1*
Leucovorin 400 mg/m² IV day 1**
5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours) IV continuous infusion
Repeat every 2 weeks

mFOLFOX7[4]
Oxaliplatin 85 mg/m² IV day 1*
Leucovorin 400 mg/m² IV day 1**
5-FU 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours) IV continuous infusion
Repeat every 2 weeks

FOLFOX + bevacizumab[5]
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

FOLFOX + panitumumab[6] (*KRAS/NRAS* WT only)
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFOX + cetuximab[7] (*KRAS/NRAS* WT only)
Cetuximab 400 mg/m² IV over 2 hours first infusion, then 250 mg/m² IV over 60 minutes weekly
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks

CAPEOX[8]
Oxaliplatin 130 mg/m² IV day 1*
Capecitabine 1000‡ mg/m² twice daily PO for 14 days
Repeat every 3 weeks

CAPEOX + bevacizumab[8]¶
Oxaliplatin 130 mg/m² IV day 1*
Capecitabine 1000‡ mg/m² PO twice daily for 14 days
Bevacizumab 7.5 mg/kg IV day 1
Repeat every 3 weeks

See References on COL-C 10 of 10

*Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Oncol Pract 2016;12:e548-553.
**Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
‡The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine.
¶Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 8 of 10)

FOLFIRI[9,10]
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1**
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion
Repeat every 2 weeks

FOLFIRI + bevacizumab[11,¶]
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

FOLFIRI + cetuximab (*KRAS/NRAS* WT only)
Cetuximab 400 mg/m² IV over 2 hours first infusion, then 250 mg/m² IV over 60 minutes weekly[12]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[13]

FOLFIRI + panitumumab[14] **(*KRAS/NRAS* WT only)**
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI + ziv-aflibercept[15]
Ziv-aflibercept 4 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI + ramucirumab[16]
Ramucirumab 8 mg/kg over 60 minutes, day 1
Repeat every 2 weeks

FOLFOXIRI[17]
Irinotecan 165 mg/m² IV day 1, oxaliplatin 85 mg/m² IV day 1,* leucovorin 400 mg/m² day 1, fluorouracil 1600 mg/m²/d x 2 days (total 3200 mg/m² over 48 hours) continuous infusion starting on day 1.**
Repeat every 2 weeks
The dose of 5-FU listed here was used in European studies. U.S. patients have been shown to have poorer tolerance for 5-FU. A starting dose of 5-FU consistent with the dose recommended in FOLFOX or FOLFIRI should be strongly considered for U.S. patients.

FOLFOXIRI + bevacizumab[18]
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

IROX[19]
Oxaliplatin 85 mg/m² IV*, followed by irinotecan 200 mg/m² over 30–90 minutes every 3 weeks

See References on COL-C 10 of 10

*Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Oncol Pract 2016;12:e548-553.
**Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
¶Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

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SYSTEMATIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 9 of 10)

Bolus or infusional 5-FU/leucovorin
Roswell Park regimen[20]
Leucovorin 500 mg/m² IV over 2 hours, days 1, 8, 15, 22, 29, and 36
5-FU 500 mg/m² IV bolus 1 hour after start of leucovorin, days 1, 8, 15, 22, 29, and 36
Repeat every 8 weeks

Simplified biweekly infusional 5-FU/LV (sLV5FU2)[9]
Leucovorin 400 mg/m² IV over 2 hours on day 1, followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion**
Repeat every 2 weeks

Weekly
Leucovorin 20 mg/m² IV over 2 hours on day 1, 5-FU 500 mg/m² IV bolus injection 1 hour after the start of leucovorin. Repeat weekly.[21]
5-FU 2600 mg/m² by 24-hour infusion plus leucovorin 500 mg/m²
Repeat every week[21]

Capecitabine[8]
Capecitabine 850–1250 mg/m² PO twice daily, days 1–14
Repeat every 3 weeks

Capecitabine + Bevacizumab[22,¶]
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

Irinotecan
Irinotecan 125 mg/m² IV over 30–90 minutes, days 1 and 8
Repeat every 3 weeks[23,24]
or Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Repeat every 2 weeks
or Irinotecan 300–350 mg/m² IV over 30–90 minutes, day 1
Repeat every 3 weeks

Irinotecan + cetuximab (*KRAS/NRAS* WT only)
Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly [25]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[13]

Cetuximab (*KRAS/NRAS* WT only)
Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly[25]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[13]

Panitumumab[26] (*KRAS/NRAS* WT only)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Regorafenib[27]
Regorafenib 160 mg§ PO daily days 1–21
Repeat every 28 days

Trifluridine + tipiracil[28]
Trifluridine + tipiracil 35 mg/m² up to a maximum dose of 80 mg per dose (based on the trifluridine component)
PO twice daily days 1–5 and 8–12
Repeat every 28 days

Pembrolizumab[29]
Pembrolizumab 2 mg/kg every 3 weeks

Nivolumab[30]
Nivolumab 3 mg/kg every 2 weeks
or Nivolumab 240 mg IV every two weeks

See References on COL-C 10 of 10

**Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
¶Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).
§It is common practice to start at a lower dose of regorafenib (80 or 120 mg) and escalate, as tolerated.

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - REFERENCES (PAGE 10 of 10)

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[10]Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol 2007;25:4779-4786.
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[12]Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-345.
[13]Martín-Martorell P, Roselló S, Rodríguez-Braun E, et al. Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. Br J Cancer 2008;99:455-458.
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PRINCIPLES OF RADIATION THERAPY

- **Radiation therapy fields should include the tumor bed, which should be defined by preoperative radiologic imaging and/or surgical clips.**
- **Radiation doses should be: 45–50 Gy in 25–28 fractions.**
  - **Consider boost for close or positive margins.**
  - **Small bowel dose should be limited to 45 Gy.**
  - **Large bowel, stomach, and liver are critical structures that should be evaluated on the dose-volume histogram (DVH).**
  - **5-FU–based chemotherapy should be delivered concurrently with radiation.**
- **If radiation therapy is to be used, conformal external beam radiation should be routinely used and intensity-modulated radiation therapy (IMRT) should be reserved only for unique clinical situations such as reirradiation of previously treated patients with recurrent disease or unique anatomical situations.**
- **Neoadjuvant radiation therapy with concurrent 5-FU-based chemotherapy may be considered for initially unresectable non-metastatic T4 colon cancer to aid resectability.**
- **Intraoperative radiation therapy (IORT), if available, may be considered for patients with T4 or recurrent cancers as an additional boost. If IORT is not available, additional 10–20 Gy external beam radiation and/or brachytherapy could be considered to a limited volume.**
- **Arterially directed catheter therapy, and in particular yttrium 90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.**
- **In patients with a limited number of liver or lung metastases, radiotherapy to the metastatic site can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3-D conformal radiation therapy, IMRT, or stereotactic body radiation therapy (SBRT).**

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PRINCIPLES OF RISK ASSESSMENT FOR STAGE II DISEASE[1,2,3]

- **Patient/physician discussion regarding the potential risks of therapy compared to potential benefits, including prognosis. This should include discussion of evidence supporting treatment, assumptions of benefit from indirect evidence, morbidity associated with treatment, high-risk characteristics, and patient preferences.**
- **When determining if adjuvant therapy should be administered, the following should be taken into consideration:**
  - **Number of lymph nodes analyzed after surgery (<12)**
  - **Poor prognostic features (eg, poorly differentiated histology [exclusive of those that are MSI-H]; lymphatic/vascular invasion; bowel obstruction; PNI; localized perforation; close, indeterminate, or positive margins)**
  - **Assessment of other comorbidities and anticipated life expectancy.**
- **The benefit of adjuvant chemotherapy does not improve survival by more than 5%.**
- **Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing**
  - **Universal MMR* or MSI* testing is recommended in all patients with a personal history of colon or rectal cancer. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal**
  - **Stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy.[4]**

*IHC for MMR and PCR for MSI are different assays measuring the same biological effect.

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PRINCIPLES OF ADJUVANT THERAPY (1 OF 2)

- **FOLFOX is superior to 5-FU/leucovorin for patients with stage III colon cancer.[1,2] Capecitabine/oxaliplatin is superior to bolus 5-FU/leucovorin for patients with stage III colon cancer. FLOX is an alternative to FOLFOX or CAPEOX but FOLFOX or CAPEOX are preferred.[3]**
- **Capecitabine appears to be equivalent to bolus 5-FU/leucovorin in patients with stage III colon cancer.[4]**
- **A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer.[5] FOLFOX is reasonable for stage II patients with multiple high-risk factors and is not indicated for good- or average-risk patients with stage II colon cancer.**
- **A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.[5]**
- **Bevacizumab, cetuximab, panitumumab, irinotecan, ziv-aflibercept, ramucirumab, regorafenib, trifluridine + tipiracil, nivolumab, or pembrolizumab should not be used in the adjuvant setting for patients with stage II or III colon cancer outside the setting of a clinical trial.**

See Principles of Adjuvant Therapy - Chemotherapy Regimens and References on COL-F 2 of 2

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PRINCIPLES OF ADJUVANT THERAPY - CHEMOTHERAPY REGIMENS AND REFERENCES (2 of 2)

mFOLFOX 6
Oxaliplatin 85 mg/m² IV, day 1*
Leucovorin 400 mg/m² IV, day 1**
5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion.
Repeat every 2 weeks.[1,2,3]

FLOX[4]
5-FU 500 mg/m² IV bolus weekly x 6 + leucovorin 500 mg/m² IV weekly x 6, each 8-week cycle x 3 with oxaliplatin 85 mg/m² IV* administered on weeks 1, 3, and 5 of each 8-week cycle x 3.

Capecitabine[5]
Capecitabine 1000-1250‡ mg/m² twice daily days 1–14 every 3 wks x 24 wks.

CAPEOX[6]
Oxaliplatin 130 mg/m² IV* day 1
Capecitabine 1000‡ mg/m² twice daily days 1–14 every 3 weeks x 24 weeks.

5-FU/leucovorin
- **Leucovorin 500 mg/m² given as a 2-hour infusion and repeated weekly x 6. 5-FU 500 mg/m² given bolus 1 hour after the start of leucovorin and repeated 6 x weekly. Every 8 weeks for 4 cycles.[7]**
- **Simplified biweekly infusional 5-FU/LV (sLV5FU2)[8]**
  Leucovorin 400 mg/m² IV day 1, followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion. Repeat every 2 weeks.**

*Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Oncol Pract 2016;12:e548-553.
**Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
‡The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine.

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PRINCIPLES OF SURVIVORSHIP - Colorectal Long-term Follow-up Care

Colorectal Cancer Surveillance:
- See COL-8
- Long-term surveillance should be carefully managed with routine good medical care and monitoring, including cancer screening, routine health care, and preventive care.
- Routine CEA monitoring and routine CT scanning are not recommended beyond 5 years.

Management of Late Sequelae of Disease or Treatment:[1-5]
See NCCN Guidelines for Survivorship
- For chronic diarrhea or incontinence
  - Consider anti-diarrheal agents, bulk-forming agents, diet manipulation, pelvic floor rehabilitation, and protective undergarments.
- For oxaliplatin-induced neuropathy
  - Consider duloxetine for painful neuropathy only, not effective for numbness, tingling, or cold sensitivity.
- For fatigue
  - Encourage physical activity, energy conservation measures

Survivorship Care Planning:
The oncologist and primary care provider should have defined roles in the surveillance period, with roles communicated to patient.[6]
- Develop survivorship care plan that includes:
  - Overall summary of treatment, including all surgeries, radiation treatments, and chemotherapy received.
  - Description of possible expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment.
  - Surveillance recommendations.
  - Delineate appropriate timing of transfer of care with specific responsibilities identified for primary care physician and oncologist.
  - Health behavior recommendations.

Cancer Screening Recommendations:
These recommendations are for average-risk patients. Recommendations for high-risk individuals should be made on an individual basis.
- Breast Cancer: NCCN Guidelines for Breast Cancer Screening
- Prostate Cancer: NCCN Guidelines for Prostate Early Detection

Counseling Regarding Healthy Lifestyle and Wellness:[7]
See NCCN Guidelines for Survivorship[1-5]
- Maintain a healthy body weight throughout life.
- Adopt a physically active lifestyle (at least 30 minutes of moderate intensity activity on most days of the week). Activity recommendations may require modification based on treatment sequelae (ie, ostomy, neuropathy).
- Consume a healthy diet with emphasis on plant sources. Diet recommendations may be modified based on severity of bowel dysfunction.
- Consider low-dose aspirin.
- Limit alcohol consumption.
- Receive smoking cessation counseling as appropriate.

Additional health monitoring and immunizations should be performed as indicated under the care of a primary care physician. Survivors are encouraged to maintain a therapeutic relationship with a primary care physician throughout their lifetime.
See NCCN Guidelines for Survivorship

See References COL-G 2 of 2

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PRINCIPLES OF SURVIVORSHIP - Colorectal Long-term Follow-up Care
References

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Table 1. Definitions for T, N, M

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria[a]
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum[b]
T4b	Tumor directly invades or is adherent to other organs or structures[b,c]
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in four or more regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in seven or more regional lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (eg, liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

Table 2. Anatomic Stage/Prognostic Groups

Stage	T	N	M	Dukes*	MAC*
0	Tis	N0	M0	-	-
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1-T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3-T4a	N1/N1c	M0	C	C2
	T2-T3	N2a	M0	C	C1/C2
	T1-T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3-T4a	N2b	M0	C	C2
	T4b	N1-N2	M0	C	C3
IVA	Any T	Any N	M1a	-	-
IVB	Any T	Any N	M1b	-	-

Note: cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (eg, ypTNM). Patients who have a complete pathologic response are ypT0N0cM0 that may be similar to Stage Group 0 or I. The r prefix is to be used for those cancers that have recurred after a disease-free interval (rTNM).

*Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (Any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

[a]Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

[b]Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (ie, respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).

[c]Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN site-specific factor should be used for perineural invasion.

Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2016, an estimated 95,270 new cases of colon cancer and approximately 39,220 cases of rectal cancer will occur. During the same year, an estimated 49,190 people will die of colon and rectal cancer combined.[1] Despite these high numbers, the incidence of colon and rectal cancers per 100,000 people decreased from 60.5 in 1976 to 46.4 in 2005.[2] In fact, the incidence of colorectal cancer decreased at a rate of approximately 3% per year between 2003 and 2012.[1] The incidence rate for colorectal cancer reported by the CDC for 2011 is 40.0 per 100,000 persons.[3] In addition, mortality from colorectal cancer decreased by almost 35% from 1990 to 2007,[4] and is currently down by about 50% from peak mortality rates.[1] These improvements in incidence of and mortality from colorectal cancer are thought to be a result of cancer prevention and earlier diagnosis through screening and better treatment modalities.

Despite the observed improvements in the overall colorectal cancer incidence rate, a retrospective cohort study of the SEER colorectal cancer registry found that the incidence of colorectal cancer in patients younger than 50 years has been increasing.[5] The authors estimate that the incidence rates for colon and rectal cancers will increase by 90.0% and 124.2%, respectively, for patients 20 to 34 years by 2030. The cause of this trend is currently unknown.

This Discussion summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer. These guidelines begin with the clinical presentation of the patient to the primary care physician or gastroenterologist and address diagnosis, pathologic staging, surgical management, perioperative treatment, patient surveillance, management of recurrent and metastatic disease, and survivorship. When reviewing these guidelines, clinicians should be aware of several things. First, these guidelines adhere to the TNM staging system (Table 1 in the guidelines).[6] Furthermore, all recommendations are classified as category 2A except where noted in the text or algorithm. Although the guidelines are believed to represent the optimal treatment strategy, the panel believes that, when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Colon Cancer, an electronic search of the PubMed database was performed to obtain key literature in the field of colorectal cancer published between June 12, 2015 and June 12, 2016, using the following search terms: (colon cancer) OR (colorectal cancer) OR (rectal cancer). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[7]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 375 citations, and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting

abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

Risk Assessment

Approximately 20% of cases of colon cancer are associated with familial clustering, and first-degree relatives of patients with colorectal adenomas or invasive colorectal cancer are at increased risk for colorectal cancer.[8-12] Genetic susceptibility to colorectal cancer includes well-defined inherited syndromes, such as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer) and familial adenomatous polyposis.[13-15] Therefore, it is recommended that all patients with colon cancer be queried regarding their family history and considered for risk assessment, as detailed in the NCCN Guidelines for Colorectal Cancer Screening (available at www.NCCN.org). Results from a recent randomized controlled trial suggest that most individuals without a personal history of colorectal cancer and with one first-degree relative with colorectal cancer diagnosed before age 50 years or two first-degree relatives with colorectal cancer diagnosed at any age can safely be screened with colonoscopy every 6 years.[16]

Lynch Syndrome

Lynch syndrome is the most common form of genetically determined colon cancer predisposition, accounting for 2% to 4% of all colorectal cancer cases.[13,14,17,18] This hereditary syndrome results from germline mutations in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). Although identifying a germline mutation in an MMR gene through sequencing is definitive for Lynch syndrome, patients usually undergo selection by considering family history and performing an initial test on tumor tissue before sequencing. One of two different initial tests can be performed on colorectal cancer specimens to identify individuals who might have Lynch syndrome: 1) immunohistochemical analysis for MMR protein expression, which is often diminished because of mutation; or 2) analysis for microsatellite instability (MSI), which results from MMR deficiency and is detected as changes in the length of repetitive DNA elements in tumor tissue caused by the insertion or deletion of repeated units.[19] Testing the *BRAF* gene for mutation is indicated when immunohistochemical analysis shows that MLH1 protein expression is absent in the tumor. The presence of a *BRAF* mutation indicates that *MLH1* gene expression is down-regulated through somatic methylation of the promoter region of the gene and not through a germline mutation.[19]

Many NCCN Member Institutions and other comprehensive cancer centers now perform immunohistochemistry (IHC) and sometimes MSI testing on all newly diagnosed colorectal and endometrial cancers regardless of family history to determine which patients should have genetic testing for Lynch syndrome.[20-23] The cost effectiveness of this approach, referred to as universal or reflex testing, has been confirmed for colorectal cancer, and this approach has been endorsed by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group at the CDC.[24-26] The US Multi-Society Task Force on Colorectal Cancer also recommends universal genetic testing of tumors of all patients with newly diagnosed colorectal cancer, as does the American Gastroenterological Association.[27,28] The Cleveland Clinic recently reported on its experiences implementing such a universal screening approach.[29]

The NCCN Colon/Rectal Cancer Panel endorses universal MMR or MSI testing of all patients with a personal history of colon or rectal cancer to

identify individuals with Lynch syndrome. An infrastructure needs to be in place to handle the screening results in either case. A more detailed discussion is available in the NCCN Guidelines for Colorectal Cancer Screening (available at www.NCCN.org).

Other Risk Factors for Colorectal Cancer

It is well-recognized that individuals with inflammatory bowel disease (ie, ulcerative colitis, Crohn's disease) are at an increased risk for colorectal cancer.[30-32] Other possible risk factors for the development of colorectal cancer include smoking, the consumption of red and processed meats, alcohol consumption, diabetes mellitus, low levels of physical activity, metabolic syndrome, and obesity/high body mass index (BMI).[31,33-53] In fact, in the EPIC cohort of almost 350,000 individuals, those who adhered to 5 healthy lifestyle factors (healthy weight, physical activity, non-smoking, limited alcohol consumption, healthy diet) had a hazard ratio (HR) for the development of colorectal cancer of 0.63 (95% CI, 0.54–0.74) compared with those who adhered to ≤1 of the factors.[54] Other large studies support the conclusion that adherence to healthy lifestyle factors can reduce the risk of colorectal cancer.[55,56]

Some data suggest that consumption of dairy may lower risk for the development of colorectal cancer.[57,58] However, a recent systematic review and meta-analysis of 15 cohort studies (>900,000 subjects; >5200 cases of colorectal cancer) only found an association between risk for colon cancer in men and the consumption of nonfermented milk.[59] No association was seen for rectal cancer in men or for colon or rectal cancer in women, and no association was seen for either cancer in either gender with consumption of solid cheese or fermented milk. Large cohort studies and meta-analyses suggest that other dietary factors may also lower the risk for colorectal cancer, including the consumption of fish and legumes.[60-62] Furthermore, the use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) may also decrease the risk for colorectal cancer.[63-68]

In addition, some data suggest that smoking, metabolic syndrome, obesity, and red/processed meat consumption are associated with a poor prognosis.[36,69-73] Conversely, post-diagnosis fish consumption may be associated with a better prognosis.[74] A family history of colorectal cancer increases risk while improving prognosis.[75] Data on the effect of dairy consumption on prognosis after diagnosis of colorectal cancer are conflicting.[76,77]

The relationship between diabetes and colorectal cancer is complex. Whereas diabetes and insulin use may increase the risk of developing colorectal cancer, treatment with metformin appears to decrease risk, at least in women.[78-85] Results of a small randomized study suggest that 1 year of low-dose metformin in non-diabetic patients with previously resected colorectal adenomas or polyps may reduce the likelihood of subsequent adenomas or polyps.[86] In addition, although patients with colorectal cancer and diabetes appear to have a worse prognosis than those without diabetes,[87] patients with colorectal cancer treated with metformin seem to have a survival benefit.[88] The data regarding the effects of metformin on colorectal cancer incidence and mortality, however, are not completely consistent, with some studies seeing no effect.[89,90]

Staging

Staging in colon cancer is based on the TNM (tumor, node, metastases) system. The TNM categories reflect very similar survival outcomes for rectal and colon cancer; these diseases therefore share the same staging system.[6]

The 8th edition of the AJCC Staging Manual was released in 2016, with implementation scheduled for January 1, 2018. In this edition, T1 tumors involve the submucosa; T2 tumors penetrate through the submucosa into the muscularis propria; T3 tumors penetrate through the muscularis propria; T4a tumors directly penetrate to the surface of the visceral peritoneum; and T4b tumors directly invade or are adherent to other organs or structures.[6] The T component of colon cancer staging is very important in prognostication, because analyses have shown that patients with T4,N0 tumors have a lower survival than those with T1-2,N1-2 tumors.[91-93] Furthermore, in an analysis of 109,953 patients with invasive colon cancer included in the SEER colon cancer database from 1992 to 2004, the relative 5-year survival rate (ie, 5-year survival corrected by age-related morbidity) was considerably higher (79.6%) for node-negative patients with T4a compared with node-negative patients with T4b tumors (58.4%).[94]

Regional lymph node classification includes N1a (1 positive lymph node); N1b (2–3 positive lymph nodes), N2a (4–6 positive nodes); and N2b (7 or more positive nodes). In addition, tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis (ie, satellite tumor nodules) have been classified as N1c. Within each T stage, survival is inversely correlated with N stage (N0, N1a, N1b, N2a, and N2b).[6]

Metastatic disease is classified as M1a when metastases are to only one site/solid organ (including to lymph nodes outside the primary tumor regional drainage area) are positive. M1b is used for metastases to multiple distant sites or solid organs, exclusive of peritoneal carcinomatosis. The 8th edition of the AJCC Cancer Staging Manual includes the M1c category for peritoneal carcinomatosis with or without blood-borne metastasis to visceral organs.[6] Patients with peritoneal metastases have a shorter progression-free survival (PFS) and overall survival (OS) than those without peritoneal involvement.[95]

Pathology

Colorectal cancers are usually staged after surgical exploration of the abdomen and pathologic examination of the surgical specimen. Some of the criteria that should be included in the report of the pathologic evaluation include the following: grade of the cancer; depth of penetration and extension to adjacent structures (T); number of regional lymph nodes evaluated; number of positive regional lymph nodes (N); an assessment of the presence of distant metastases to other organs, to the peritoneum or an abdominal structure, or in non-regional lymph nodes (M); the status of proximal, distal, radial, and mesenteric margins; lymphovascular invasion; perineural invasion (PNI); and tumor deposits.[6,96-104] The prefixes “p” and “yp” used in TNM staging denote “pathologic staging” and “pathologic staging after neoadjuvant therapy and surgery,” respectively.[6]

Margins

In colon cancer, the radial margin (or circumferential resection margin, CRM) represents the adventitial soft tissue closest to the deepest penetration of the tumor. It is created surgically by blunt or sharp dissection of the retroperitoneal aspect, and it corresponds to any aspect of the colon that is not covered by a serosal layer of mesothelial cells.[6] It must be dissected from the retroperitoneum to remove the viscus. The serosal (peritoneal) surface does not constitute a surgical margin. The radial margins should be assessed in all colonic segments with non-peritonealized surfaces. In segments of the colon that are completely encased by peritoneum, such as the transverse colon, the mesenteric resection margin is the only relevant radial margin.[6] On pathologic examination, it is difficult to appreciate the demarcation

between the peritonealized surface and the non-peritonealized surface. The surgeon is therefore encouraged to mark the area of non-peritonealized surface with a clip or suture.[6] In a study of 608 patients with rectal cancer, a positive radial margin was shown to be a negative prognostic factor for both local recurrence and OS.[105] Patients with CRM-positive resections had a 38.2% local recurrence rate, whereas those with CRM-negative resections had a 10.0% local recurrence rate.[105]

Lymph Nodes

The number of lymph nodes evaluated is important to note on the pathology report. A secondary analysis of patients from the Intergroup Trial INT-0089 showed that an increase in the number of lymph nodes examined was associated with increased survival for patients with both node-negative and node-positive disease.[106] In addition, results from population-based studies show an association between improvement in survival and examination of greater than or equal to 12 lymph nodes.[107,108] The mechanism for this correlation is poorly understood. It has been hypothesized that the analysis of more lymph nodes would result in more accurate staging and thus better tailored treatments, but recent results suggest that this idea is not correct.[109-111] Instead it is likely that other factors associated with lymph node harvest are important for the survival advantage. For instance, the extent and quality of surgical resection can have an impact on the node harvest.[112] The number of regional lymph nodes retrieved from a surgical specimen also varies with age of the patient, gender, and tumor grade or site.[106,107,113,114] In addition, it has been suggested that lymph nodes in patients with a strong anti-cancer immune response are easier to find, and that such patients have an improved prognosis.[115] Another possibility is that the underlying tumor biology affects lymph node yield and prognosis in parallel. For instance, MSI and wild-type *KRAS/BRAF* have been associated with both improved prognosis and increased lymph node retrieval.[116,117]

Regardless of the mechanism for the observed correlation, the panel recommends examination of a minimum of 12 lymph nodes. This recommendation is supported by the College of American Pathologists (CAP)[118] and the 8th edition of the AJCC Cancer Staging Manual,[6] which also specify pathologic examination of a minimum of 12 lymph nodes. Notably, emerging evidence suggests that a greater number of nodes may need to be examined in some situations, particularly for T4 lesions, to provide an adequate assessment of disease stage.[119] For stage II (pN0) colon cancer, it is recommended that the pathologist go back to the specimen and submit more tissue of potential lymph nodes if fewer than 12 nodes were initially identified. Patients considered to have N0 disease but for whom less than 12 nodes have been examined are suboptimally staged and should be considered to be at higher risk.

The ratio of positive lymph nodes to the total number of lymph nodes examined is also being evaluated for possible prognostic impact. Case series have suggested cutoffs of 0.1, 0.2, or 0.25 as lymph node ratios that are prognostic for OS or PFS.[120-123] A systematic review and meta-analysis of 33 studies that included >75,000 patients with node-positive colorectal cancer concluded that a higher lymph node ratio was significantly associated with shorter OS and disease-free survival (DFS).[124] Analysis of the SEER database, however, suggests that the lymph node ratio does not adequately represent the different effects of both the number of positive lymph nodes and the number of lymph nodes examined.[125]

The potential benefit of sentinel lymph node evaluation for colon cancer has mostly been associated with providing more accurate staging of nodal pathology through detection of micrometastatic disease in the

sentinel node(s).[126] Results of studies evaluating the sentinel node for micrometastatic disease through use of hematoxylin and eosin (H&E) staining to identify small foci of tumor cells and the identification of particular tumor antigens through immunohistochemical analysis have been reported.[126-131]

There is also potential benefit of assessing regional lymph nodes for isolated tumor cells.[129,132-135] The 8th edition of the AJCC Cancer Staging Manual considers tumor clusters smaller than 0.2 mm to be true metastases because such micrometastases have been shown to be a poor prognostic factor.[6] One study of 312 consecutive patients with pN0 disease found that positive cytokeratin staining was associated with a higher risk of recurrence.[136] Relapse occurred in 14% of patients with positive nodes compared to 4.7% of those with negative nodes (HR, 3.00; 95% CI, 1.23–7.32; *P* = .013). A 2012 systematic review and meta-analysis came to a similar conclusion, finding decreased survival in patients with pN0 tumors with immunohistochemical or reverse transcriptase polymerase chain reaction (RT-PCR) evidence of tumor cells in regional nodes.[137] A 2014 meta-analysis also found that the presence of micrometastases increases the likelihood of disease recurrence.[138]

Tumor Deposits

Tumor deposits, also called extranodal tumor deposits, peritumoral deposits, or satellite nodules, are irregular discrete tumor deposits in the pericolic or perirectal fat that show no evidence of residual lymph node tissue, but are within the lymphatic drainage of the primary tumor. They are not counted as lymph nodes replaced by tumor. Most of these tumor deposits are thought to arise from lymphovascular invasion or, occasionally, PNI.[139,140] The number of tumor deposits should be recorded in the pathology report, because they have been shown to be associated with reductions in DFS and OS.[103,104,141,142] Multivariate survival analysis in one study showed that patients with pN0 tumors without satellite nodules had a 91.5% 5-year survival rate compared with a 37.0% 5-year survival rate for patients with pN0 tumors and the presence of satellite nodules (*P* < .0001).[104]

Perineural Invasion

Several studies have shown that the presence of PNI is associated with a significantly worse prognosis.[100-102,141,143-146] For example, one retrospective analysis of 269 consecutive patients who had colorectal tumors resected at one institution found a 4-fold greater 5-year survival in patients without PNI versus patients whose tumors invaded nearby neural structures.[101] Multivariate analysis of patients with stage II rectal cancer showed that patients with PNI have a significantly worse 5-year DFS compared with those without PNI (29% vs. 82%; *P* = .0005).[102] Similar results were seen for patients with stage III disease.[100] A meta-analysis that included 58 studies and 22,900 patients also found that PNI is associated with a worse 5-year OS (RR, 2.09; 95% CI, 1.68–2.61) and 5-year DFS (RR, 2.35; 95% CI, 1.66–3.31).[144] PNI is therefore included as a high-risk factor for systemic recurrence.

The Role of Vitamin D in Colorectal Cancer

Prospective studies have suggested that vitamin D deficiency may contribute to colorectal cancer incidence and/or that vitamin D supplementation may decrease colorectal cancer risk.[147-151] Furthermore, several prospective studies have shown that low vitamin D levels are associated with increased mortality of patients with colorectal cancer.[152-155] In fact, a systematic review and meta-analysis of 5 studies totaling 2330 patients with colorectal cancer compared the outcomes of patients in the highest and lowest categories of vitamin D levels and found better OS (HR, 0.71; 95% CI, 0.55–0.91) and disease-specific

mortality (HR, 0.65; 95% CI, 0.49–0.86) in those with higher vitamin D levels.[156] Another meta-analysis determined that the relationship between vitamin D levels and mortality is linear.[157]

Results of a recent randomized, double-blind, placebo-controlled trial, however, showed that supplementation with vitamin D and/or calcium had no effect on the recurrence of colorectal adenomas within 3 to 5 years after removal of adenomas in 2259 participants.[158] Furthermore, no study has yet examined whether vitamin D supplementation improves outcomes in patients with colorectal cancer. In a 2010 report, the Institute of Medicine concluded that data supporting a role for vitamin D were only conclusive in bone health and not in cancer and other diseases.[159] Citing this report and the lack of level 1 evidence, the panel does not currently recommend routine screening for vitamin D deficiency or supplementation of vitamin D in patients with colorectal cancer.

Adenocarcinomas of the Small Bowel and Appendix

Adenocarcinomas of the small bowel or appendix are rare cancers for which no NCCN Guidelines exist. Localized small bowel adenocarcinomas are treated with surgical resection, but local and distant recurrences are common and optimal perioperative therapy is unknown.[160] The use of perioperative chemotherapy with or without radiation has been addressed mainly with retrospective reports.[161-166] Neoadjuvant chemoradiation was studied in one phase II trial that included patients with duodenal or pancreatic adenocarcinomas.[167] Four of 5 patients with tumors in the duodenum were able to undergo resection. Another small prospective study evaluated neoadjuvant chemoradiation in patients with duodenal or pancreatic adenocarcinomas.[168] All 4 patients with duodenal cancer underwent curative resection and experienced a complete pathologic response.

Data regarding therapy for advanced adenocarcinoma of the small bowel or appendix are also limited mostly to retrospective reports.[169,170] One small prospective phase II study evaluated capecitabine/oxaliplatin (CapeOx) for treatment of advanced adenocarcinomas of the small bowel and ampulla of Vater.[171] The overall response rate (ORR) (the primary endpoint) was 50%, with 10% achieving complete response. A similar response rate (48.5%) was seen in another small phase II study that assessed the efficacy of FOLFOX (infusional 5-FU, LV, oxaliplatin) in first-line treatment of advanced small bowel cancer.[172] These response rates to CapeOx and FOLFOX were much higher than the 18% response rate seen in another small phase II study that evaluated 5-FU/doxorubicin/mitomycin C in patients with metastatic small bowel adenocarcinomas.[173]

Data on treatment of appendiceal adenocarcinomas are also quite limited. Most patients receive debulking surgery with systemic or intraperitoneal therapy (intraperitoneal therapy is discussed further in *Peritoneal Carcinomatosis*, below). Case series have shown that systemic combination chemotherapy in patients with advanced disease can result in response rates similar to those seen in advanced colorectal cancer.[174-176] A recent analysis of the NCCN Outcomes Database found that fluoropyrimidine-based therapy is the most commonly administered systemic therapy at NCCN Member Institutions.[177] Among 99 patients with a recorded best response, the response rate was 39%, with a median PFS of 1.2 years.

Acknowledging the lack of high-level data, the panel recommends that adenocarcinomas of the small bowel or appendix be treated with systemic chemotherapy according to these NCCN Guidelines for Colon Cancer.

Clinical Presentation and Treatment of Nonmetastatic Disease

Workup and Management of the Malignant Polyp

A malignant polyp is defined as one with cancer invading the submucosa (pT1). Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated the submucosa and are therefore not considered capable of regional nodal metastasis.[97] The panel recommends marking the polyp site during colonoscopy or within 2 weeks of the polypectomy if deemed necessary by the surgeon.

Before making a decision about surgical resection for an endoscopically resected adenomatous polyp or adenoma, physicians should review the pathology and consult with the patient.[178] In patients with invasive cancer in a pedunculated or sessile polyp (adenoma), no additional surgery is required if the polyp has been completely resected and has favorable histologic features.[179,180] Favorable histologic features include lesions of grade 1 or 2, no angiolymphatic invasion, and a negative resection margin. However, in addition to the option of observation, the panel includes the option of colectomy in patients with a completely removed, single-specimen, sessile polyp with favorable histologic features and clear margins. This option is included because the literature seems to indicate that patients with sessile polyps may have a significantly greater incidence of adverse outcomes, including disease recurrence, mortality, and hematogenous metastasis compared with those with pedunculated polyps. This increased incidence likely occurs because of the high probability of a positive margin after endoscopic removal.[181-183]

If the polyp specimen is fragmented, the margins cannot be assessed, or the specimen shows unfavorable histopathology, colectomy with en bloc removal of lymph nodes is recommended.[178,184-186] Laparoscopic surgery is an option.[187] Unfavorable histopathologic features for malignant polyps include grade 3 or 4, angiolymphatic invasion, or a positive margin of resection.[188,189] Notably, no consensus currently exists as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as the presence of tumor within 1 to 2 mm of the transected margin or the presence of tumor cells within the diathermy of the transected margin.[178,190-192] In addition, several studies have shown that tumor budding is an adverse histologic feature associated with adverse outcome and may preclude polypectomy as an adequate treatment of endoscopically removed malignant polyps.[193-196]

All patients who have malignant polyps removed by transanal excision or transabdominal resection should undergo total colonoscopy to rule out other synchronous polyps, and should subsequently undergo appropriate follow-up surveillance endoscopy. Adjuvant chemotherapy is not recommended for patients with stage I lesions.

Workup and Management of Invasive Nonmetastatic Colon Cancer

Patients who present with invasive colon cancer appropriate for resection require a complete staging workup, including pathologic tissue review, total colonoscopy, CBC, chemistry profile, carcinoembryonic antigen (CEA) determination, and baseline CT scans of the chest, abdomen, and pelvis.[197] CT should be with IV and oral contrast. If the CT of the abdomen and pelvis is inadequate or if CT with IV contrast is contraindicated, an abdominal/pelvic MRI with contrast plus a non-contrast chest CT should be considered. The chest CT can identify lung metastases, which occur in approximately 4% to 9% of patients with colon and rectal cancer.[198-200] One series of 378 patients found that resection of pulmonary metastases resulted in 3-year recurrence-free survival of 28% and 3-year OS of 78%.[201]

The consensus of the panel is that a PET/CT scan is not indicated at baseline for preoperative workup. In fact, PET/CT scans are usually done without contrast and multiple slicing and do not obviate the need for a contrast-enhanced diagnostic CT scan. If, however, abnormalities are seen on CT or MRI scan that are considered suspicious but inconclusive for metastases, then a PET/CT scan may be considered to further delineate that abnormality, if this information will change management. A PET/CT scan is not indicated for assessing subcentimeter lesions, because these are routinely below the level of PET/CT detection.

For resectable colon cancer that is causing overt obstruction, one-stage colectomy with en bloc removal of regional lymph nodes, resection with diversion, or diversion or stent (in selected cases) followed by colectomy are options. Stents are generally reserved for cases of distal lesions in which a stent can allow decompression of the proximal colon with later elective colostomy with primary anastomosis.[202] A recent meta-analysis found that oncologic outcomes were similar for surgery and for stenting followed by elective surgery.[203] Another meta-analysis of comparative studies compared colectomy to diversion followed by colectomy.[204] Although 30-day mortality and morbidity were the same between the groups, the diversion group was less likely to have a permanent colostomy (OR, 0.22; 95% CI, 0.11–0.46).

If the cancer is locally unresectable or the patient is medically inoperable, chemotherapy or chemoradiation is recommended, possibly with the goal of converting the lesion to a resectable state.

Surgical Management

For resectable non-metastatic colon cancer, the preferred surgical procedure is colectomy with en bloc removal of the regional lymph nodes.[205,206] The extent of colectomy should be based on the tumor location, resecting the portion of the bowel and arterial arcade containing the regional lymph nodes. Other nodes, such as those at the origin of the vessel feeding the tumor (ie, apical lymph node), and suspicious lymph nodes outside the field of resection, should also be biopsied or removed if possible. Resection must be complete to be considered curative, and positive lymph nodes left behind indicate an incomplete (R2) resection.[207]

There has been some recent attention focused on the quality of colectomy.[208] A retrospective observational study found a possible OS advantage for surgery in the mesocolic plane over surgery in the muscularis propria plane.[209] A comparison of resection techniques by expert surgeons in Japan and Germany showed that complete mesocolic excision (CME) with central vascular ligation resulted in greater mesentery and lymph node yields than the Japanese D3 high tie surgery.[210] Differences in outcomes were not reported. A retrospective, population-based study in Denmark also supports the benefit of a CME approach in patients with stage I-III colon cancer, with a significant difference in 4-year DFS (P = .001) between those undergoing CME resection (85.8%; 95% CI, 81.4–90.1) and those undergoing conventional resection (75.9%, 95% CI, 72.2–79.7).[211] A systematic review found that 4 of 9 prospective studies reported improved lymph node harvest and survival with CME compared with non-CME colectomy; the other studies reported improved specimen quality.[212]

Minimally Invasive Approaches to Colectomy

Laparoscopic colectomy is an option in the surgical management of colon cancer.[213-216] In a small European randomized trial (Barcelona), the laparoscopic approach seemed to be associated with some modest survival advantage, significantly faster recovery, and shorter hospital stays.[217] More recently, a similar but larger trial (COLOR trial) of 1248 patients with colon cancer randomly assigned to curative surgery with

either a conventional open approach or laparoscopic-assisted surgery showed a nonsignificant absolute difference of 2.0% in 3-year DFS favoring open colectomy.[218] Non-inferiority of the laparoscopic approach could not be established because of study limitations.[218] In the CLASICC study of 794 patients with colorectal cancer, no statistically significant differences in 3-year rates of OS, DFS, and local recurrence were observed between these surgical approaches.[219] Long-term follow-up of participants in the CLASICC trial showed that the lack of differences in outcomes between arms continued over a median 62.9 months.[220]

In another trial (COST study) of 872 patients with colon cancer randomly assigned to undergo either open or laparoscopic-assisted colectomy for curable colon cancer, similar 5-year recurrence and 5-year OS rates were seen after a median of 7 years follow-up.[221,222] A similar randomized controlled trial in Australia and New Zealand also found no differences in disease outcomes.[223] In addition, results of several recent meta-analyses have supported the conclusion that the 2 surgical approaches provide similar long-term outcomes with respect to local recurrence and survival in patients with colon cancer.[224-229] Factors have been described that may confound conclusions drawn from randomized studies comparing open colectomy with laparoscopic-assisted surgery for colon cancer.[230,231]

A subanalysis of results from the COLOR trial evaluating short-term outcomes (eg, conversion rate to open colectomy, number of lymph nodes collected, number of complications) based on hospital case volume indicated that these outcomes were statistically significantly more favorable when laparoscopic surgery was performed at hospitals with high case volumes.[232] A meta-analysis of 18 studies (6153 patients) found a lower rate of cardiac complications with laparoscopic colectomy compared with open resection.[233] Analyses of large national databases also support the benefits of the laparoscopic approach.[234,235]

In recent years, perioperative care has improved, with reductions in the average length of hospital stay and complication rates after surgery.[236,237] The multicenter, randomized, controlled EnROL trial therefore compared conventional and laparoscopic colectomy with an enhanced recovery program in place.[238] Outcomes were the same in both arms, with the exception of median length of hospital stay, which was significantly shorter in the laparoscopic group (5 days vs. 7 days; $P = .033$).

Robotic colectomy has been compared to the laparoscopic approach, mostly with observational cohort studies.[239-242] In general, the robotic approach appears to result in longer operating times and is more expensive but may be associated with less blood loss, shorter time to recovery of bowel function, shorter hospital stays, and lower rates of complications and infections.

The panel recommends that minimally invasive colectomy be considered only by surgeons experienced in the techniques. A thorough abdominal exploration is required as part of the procedure. Routine use of minimally invasive colon resection is not currently recommended for tumors that are acutely obstructed or perforated or tumors that are clearly locally invasive into surrounding structures (ie, T4). Patients at high risk for prohibitive abdominal adhesions should not have minimally invasive colectomy, and those who are found to have prohibitive adhesions during exploration should be converted to an open procedure.[187,243,244]

Adjuvant Chemotherapy for Resectable Colon Cancer

Choices for adjuvant therapy for patients with resected, nonmetastatic colon cancer depend on the stage of disease:

- Patients with stage I disease and patients with MSI-high [MSI-H], low-risk stage II disease do not require any adjuvant therapy.
- Patients with low-risk stage II disease can be enrolled in a clinical trial, observed without adjuvant therapy, or considered for capecitabine or 5-FU/leucovorin (LV). Based on results of the MOSAIC trial,[245-247] and the possible long-term sequelae of oxaliplatin-based chemotherapy, the panel does not consider FOLFOX (infusional 5-FU, LV, oxaliplatin) to be an appropriate adjuvant therapy option for patients with stage II disease without high-risk features.
- Patients with high-risk stage II disease, defined as those with poor prognostic features, including T4 tumors (stage IIB/IIC); poorly differentiated histology (exclusive of those cancers that are MSI-H); lymphovascular invasion; PNI; bowel obstruction; lesions with localized perforation or close, indeterminate, or positive margins; or inadequately sampled nodes (<12 lymph nodes), can be considered for adjuvant chemotherapy with 5-FU/LV, capecitabine, FOLFOX, capecitabine/oxaliplatin (CapeOx), or bolus 5-FU/LV/oxaliplatin (FLOX).[98,248] Observation without adjuvant therapy is also an option in this population. The factors in decision making for stage II adjuvant therapy are discussed in more detail below.
- For patients with stage III disease, the panel recommends 6 months of adjuvant chemotherapy after primary surgical treatment.[249] The treatment options are FOLFOX[245-247,250] or CapeOx[251,252] (both category 1 and preferred); FLOX (category 1)[250]; or single-agent capecitabine[253] or 5-FU/LV in patients for whom oxaliplatin therapy is believed to be inappropriate.[254-257]

The panel recommends against the use of bevacizumab, cetuximab, panitumumab, irinotecan, ziv-aflibercept, ramucirumab, regorafenib, trifluridine + tipiracil, nivolumab, or pembrolizumab in adjuvant therapy for nonmetastatic disease outside the setting of a clinical trial.
Population and institutional studies have shown that patients with resected colon cancer treated with adjuvant therapy have a survival advantage over those not treated with adjuvant therapy.[258-260] For example, patients from the National Cancer Data Base with stage III or high-risk stage II disease treated according to these NCCN Guidelines had a survival advantage over patients whose treatment did not adhere to these guidelines.[258] A retrospective cohort study of 852 patients with any stage of colon or rectal cancer treated at Memorial University Medical Center in Savannah, Georgia similarly found that concordance with the recommendations in these NCCN Guidelines resulted in a lower risk of death.[260]

Endpoints for Adjuvant Chemotherapy Clinical Trials

The Adjuvant Colon Cancer End Points (ACCENT) collaborative group evaluated the appropriateness of various endpoints for adjuvant chemotherapy trials in colon cancer. Results of an analysis of individual patient data from 20,898 patients in 18 randomized colon adjuvant clinical trials by the ACCENT group suggested that DFS after 2 and 3 years follow-up are appropriate endpoints for clinical trials involving treatment of colon cancer with 5-FU-based chemotherapy in the adjuvant setting.[261] An update of this analysis showed that most relapses occur within 2 years after surgery, and that recurrence rates were less than 1.5% per year and less than 0.5% per year after 5 and 8 years, respectively.[262] More recently, however, a further update of the

data suggested that the association between 2- or 3-year DFS and 5-year OS was reduced when patient survival after recurrence was hypothetically prolonged to match the current time to survival from recurrence seen with modern combination therapies (2 years), and that more than 5 years may now be required to evaluate the effect of adjuvant therapies on OS.[263] Further confirmation of this result comes from new analysis by the ACCENT group of data from 12,676 patients undergoing combination therapies from 6 trials.[264] This study determined that 2- and 3-year DFS correlated with 5- and 6-year OS in patients with stage III disease but not in those with stage II disease. In all patients, the correlation of DFS to OS was strongest at 6-year follow-up, suggesting that at least 6 years are required for adequate assessment of OS in modern adjuvant colon cancer trials.[264]

Adjuvant Chemotherapy in Stage II Disease

The impact of adjuvant chemotherapy for patients with stage II colon cancer has been addressed in several clinical trials and practice-based studies.[98,245-248] Results from a 2015 meta-analysis of 25 high-quality studies showed that 5-year DFS in patients with stage II colon cancer who did not receive adjuvant therapy was 81.4% (95% CI, 75.4–87.4), whereas it was 79.3% (95% CI, 75.6–83.1) for patients with stage II colon cancer treated with adjuvant chemotherapy.[265] On the other hand, for patients with stage III colon cancer, the 5-year DFS was 49.0% (95% CI, 23.2–74.8) and 63.6% (95% CI, 59.3–67.9) in those treated without and with adjuvant chemotherapy, respectively. These results suggest that the benefit of adjuvant therapy is greater in patients at higher risk because of nodal status. In contrast to results from most other trials, the QUASAR trial indicated a small but statistically significant survival benefit for patients with stage II disease treated with 5-FU/LV compared to patients not receiving adjuvant therapy (relative risk [RR] of recurrence at 2 years, 0.71; 95% CI, 0.54–0.92; P = .01).[266] In this trial, however, approximately 64% of patients had fewer than 12 lymph nodes sampled, and thus may actually have been patients with higher risk disease who were more likely to benefit from adjuvant therapy.[267]

The benefit of oxaliplatin in adjuvant therapy for patients with stage II colon cancer has also been addressed. Results from a recent post-hoc exploratory analysis of the MOSAIC trial did not show a significant DFS benefit of FOLFOX over 5-FU/LV for patients with stage II disease at a follow-up of 6 years (HR, 0.84; 95% CI, 0.62–1.14; P = .258).[268] After longer follow-up, no difference in 10-year OS was observed in the stage II subpopulation (79.5% vs. 78.4%; HR, 1.00; P = .98).[247] In addition, patients with high-risk stage II disease (ie, disease characterized by at least one of the following: T4 tumor; tumor perforation; bowel obstruction; poorly differentiated tumor; venous invasion; <10 lymph nodes examined) receiving FOLFOX did not have improved DFS compared with those receiving infusional 5-FU/LV (HR, 0.72; 95% CI, 0.50–1.02; P = .063). Furthermore, no OS benefit was seen in the stage II population overall or in the stage II population with high-risk features. Similar results were seen in the C-07 trial, which compared FLOX to 5-FU/LV in patients with stage II and III disease.[269] Results of a large population-based study also support the lack of benefit to the addition of oxaliplatin to adjuvant regimens for patients with stage II colon cancer.[270]

Clinical trial results are supported by data from the community setting. Using the SEER databases, a 2002 analysis of outcomes of patients with stage II disease based on whether they had or had not received adjuvant chemotherapy showed no statistically significant difference in 5-year OS between the groups (78% vs. 75%, respectively), with an HR for survival of 0.91 (95% CI, 0.77–1.09) when patients receiving adjuvant treatment were compared with untreated patients.[271] In contrast, a 2016 analysis of 153,110 patients with stage II colon cancer

from the National Cancer Data Base found that adjuvant treatment was associated with improved survival (HR, 0.76; $P < .001$) even after adjustment for comorbidity and unplanned hospital readmissions.[270] Results of another population-level analysis from the Netherlands published in 2016 suggest that the benefit of adjuvant therapy in patients with stage II colon cancer may be limited to those with pT4 tumors.[272]

Decision making regarding the use of adjuvant therapy for patients with stage II disease should incorporate patient/physician discussions individualized for the patient, and should include explanations of the specific characteristics of the disease and its prognosis and the evidence related to the efficacy and possible toxicities associated with treatment, centering on patient choice.[248,273,274] Observation and participation in a clinical trial are options that should be considered. Patients with average-risk stage II colon cancer have a very good prognosis, so the possible benefit of adjuvant therapy is small. Patients with high-risk features, on the other hand, traditionally have been considered more likely to benefit from adjuvant chemotherapy. However, the current definition of high-risk stage II colon cancer is clearly inadequate, because many patients with high-risk features do not have a recurrence while some patients deemed to be average-risk do.[275] Furthermore, no data point to features that are predictive of benefit from adjuvant chemotherapy, and no data correlate risk features and selection of chemotherapy in patients with high-risk stage II disease.

Overall, the NCCN Panel supports the conclusion of a 2004 ASCO Panel and believes that it is reasonable to accept the relative benefit of adjuvant therapy in stage III disease as indirect evidence of benefit for stage II disease, especially for those with high-risk features.[248] Additional information that may influence adjuvant therapy decisions in stage II and/or stage III disease (MSI, multigene assays, and the influence of patient age) is discussed below. Research into additional possible predictive markers may allow for more informed decision making in the future.[276,277]

Microsatellite Instability

MSI is an important piece of information to consider when deciding whether to use adjuvant chemotherapy in patients with stage II disease. Mutation of MMR genes or modifications of these genes (eg, methylation) can result in MMR protein deficiency and MSI (see *Risk Assessment*, above).[278] Tumors showing the presence of MSI are classified as either MSI-H or MSI-low (MSI-L), depending on the extent of instability in the markers tested, whereas tumors without this characteristic are classified as microsatellite-stable (MSS).[279] Patients determined to have defective MMR (dMMR) status are biologically the same population as those with MSI-H status.

Germline mutations in the MMR genes *MLH1*, *MSH2*, *MSH6*, and/or *PMS2* or *EpCAM* are found in individuals with Lynch syndrome, which is responsible for 2% to 4% of colon cancer cases.[13,14,17,18] Somatic MMR defects have been reported to occur in approximately 19% of colorectal tumors,[280] whereas others have reported somatic hypermethylation of the *MLH1* gene promoter, which is associated with *MLH1* gene inactivation, in as many as 52% of colon tumors.[281]

Data from the PETACC-3 trial showed that tumor specimens characterized as MSI-H are more common in stage II disease than in stage III disease (22% vs. 12%, respectively; $P < .0001$).[282] In another large study, the percentage of stage IV tumors characterized as MSI-H was only 3.5%.[283] These results suggest that MSI-H (ie, dMMR) tumors have a decreased likelihood to metastasize. In fact, substantial evidence shows that in patients with stage II disease, a deficiency in

MMR protein expression or MSI-H tumor status is a prognostic marker of a more favorable outcome.[284-286] In contrast, the favorable impact of dMMR on outcomes seems to be more limited in stage III colon cancer and may vary with primary tumor location.[284,287]

Some of these same studies also show that a deficiency in MMR protein expression or MSI-H tumor status may be a predictive marker of decreased benefit and possibly a detrimental impact from adjuvant therapy with a fluoropyrimidine alone in patients with stage II disease.[285,286,288] A retrospective study involving long-term follow-up of patients with stage II and III disease evaluated according to MSI tumor status showed that those characterized as MSI-L or MSS had improved outcomes with 5-FU adjuvant therapy. However, patients with tumors characterized as MSI-H did not show a statistically significant benefit from 5-FU after surgery, instead exhibiting a lower 5-year survival rate than those undergoing surgery alone.[285] Similarly, results from another retrospective study of pooled data from adjuvant trials by Sargent et al[286] showed that in tumors characterized as dMMR, adjuvant 5-FU chemotherapy seemed to be detrimental in patients with stage II disease, but not in those with stage III disease.

In contrast to the findings of Sargent et al,[286] however, a recent study of 1913 patients with stage II colorectal cancer from the QUASAR study, half of whom received adjuvant chemotherapy, showed that although dMMR was prognostic (the recurrence rate of dMMR tumors was 11% vs. 26% for MMR-proficient tumors), it did not predict benefit or detrimental impact of chemotherapy.[267] A recent study of patients in the CALGB 9581 and 89803 trials came to a similar conclusion.[289] MMR status was prognostic but not predictive of benefit or detrimental impact of adjuvant therapy (irinotecan plus bolus 5-FU/LV [IFL regimen]) in patients with stage II colon cancer.

The panel recommends universal MMR or MSI testing for all patients with a personal history of colon or rectal cancer to identify individuals with Lynch syndrome (see *Lynch Syndrome*, above), to inform use of immunotherapy in patients with metastatic disease (*see Pembrolizumab and Nivolumab*, below), and to inform decisions for patients with stage II disease. Patients with stage II MSI-H tumors may have a good prognosis and do not benefit from 5-FU adjuvant therapy, and adjuvant therapy should not be given to patients with low-risk stage II MSI-H tumors. It should be noted that poorly differentiated histology is not considered a high-risk feature for patients with stage II disease whose tumors are MSI-H.

Molecular Classification of Colon and Rectal Cancer

Colorectal cancer is a heterogeneous disease. An international consortium has recently reported a molecular classification, defining four different subtypes: CMS1 (MSI Immune), hypermutated, microsatellite unstable (see *Microsatellite Instability*, above), with strong immune activation; CMS2 (Canonical), epithelial, chromosomally unstable, with marked WNT and MYC signalling activation; CMS3 (Metabolic), epithelial, with evident metabolic dysregulation; and CMS4 (Mesenchymal), prominent transforming growth factor β activation, stromal invasion, and angiogenesis.[290] However, this classification is not yet recommended in clinical practice.

Multigene Assays

Several multigene assays have been developed in hopes of providing prognostic and predictive information to aid in decisions regarding adjuvant therapy in patients with stage II or III colon cancer.[275]

Oncotype DX colon cancer assay quantifies the expression of 7 recurrence-risk genes and 5 reference genes as a prognostic classifier of low, intermediate, or high likelihood of recurrence.[291] Clinical

validation in patients with stage II and III colon cancer from QUASAR[292] and National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07[293] trials showed that recurrence scores are prognostic for recurrence, DFS, and OS in stage II and III colon cancer, but are not predictive of benefit to adjuvant therapy. For the low, intermediate, and high recurrence risk groups, recurrence at 3 years was 12%, 18%, and 22%, respectively.[292] Multivariate analysis showed that recurrence scores were related to recurrence independently from TNM staging, MMR status, tumor grade, and number of nodes assessed in both stage II and III disease. Similar results were found in a recent prospectively designed study that tested the correlation between recurrence score using the Oncotype DX colon cancer assay and the risk of recurrence in patients from the CALGB 9581 trial (stage II disease).[294] An additional prospectively designed clinical validation study in patients from the NSABP C-07 trial found that the assay results correlated with recurrence, DFS, and OS.[293] This study also found some evidence that patients with higher recurrence scores may derive more absolute benefit from oxaliplatin, although the authors noted that the recurrence score is not predictive of oxaliplatin efficacy in that it does not identify patients who will or will not benefit from oxaliplatin treatment. An additional study validated the recurrence score in patients with stage II/III colon cancer treated with surgery alone.[295]

ColoPrint quantifies the expression of 18 genes as a prognostic classifier of low versus high recurrence risk.[296] In a set of 206 patients with stage I through III colorectal cancer, the 5-year relapse-free survival rates were 87.6% (95% CI, 81.5%–93.7%) and 67.2% (95% CI, 55.4%–79.0%) for those classified as low and high risk, respectively. In patients with stage II disease in particular, the HR for recurrence between the high and low groups was 3.34 (P = .017).[296] This assay was further validated in a pooled analysis of 416 patients with stage II disease, 301 of whom were assessed as a T3/MSS subset.[297] In the T3/MSS subset, patients classified as low risk and high risk had 5-year risk of relapse (survival until first event of recurrence or death from cancer) of 22.4% and 9.9%, respectively (HR, 2.41; P = .005). As with the Oncotype DX colon cancer assay, recurrence risk determined by ColoPrint is independent of other risk factors, including T stage, perforation, number of nodes assessed, and tumor grade. This assay is being further validated for its ability to predict 3-year relapse rates in patients with stage II colon cancer in a prospective trial (NCT00903565).

ColDx is a microarray-based multigene assay that uses 634 probes to identify patients with stage II colon cancer at high risk of recurrence.[298] In a 144-sample independent validation set, the HR for identification of patients with high-risk disease was 2.53 (95% CI, 1.54–4.15; P < .001) for recurrence and 2.21 (95% CI, 1.22–3.97; P = .0084) for cancer-related death. A cohort study of patients in the C9581 trial found that patients with stage II colon cancer identified as high risk by ColDx had a shorter recurrence-free interval than those identified as low-risk (multivariable HR, 2.13; 95% CI, 1.3–3.5; P < .01).[299] Similar to the other assays described here, the recurrence risk determined by ColDx is independent of other risk factors.

In summary, the information from these tests can further inform the risk of recurrence over other risk factors, but the panel questions the value added. Furthermore, there is no evidence of predictive value in terms of the potential benefit of chemotherapy to any of the available multigene assays. The panel believes that there are insufficient data to recommend the use of multigene assays to determine adjuvant therapy.

Adjuvant Chemotherapy in Elderly Patients

Adjuvant chemotherapy usage declines with the age of the patient.[300] Questions regarding the safety and efficacy of chemotherapy in older patients have been difficult to answer, because older patients are underrepresented in clinical trials. Some data speaking to these questions have been reviewed.[301-303]

Population studies have found that adjuvant therapy is beneficial in older patients. A retrospective analysis of 7263 patients from the linked SEER-Medicare Databases found a survival benefit for the use of 5-FU/LV in patients 65 years or older with stage III disease (HR, 0.70; $P < .001$).[304] Another analysis of 5489 patients aged greater than or equal to 75 years diagnosed with stage III colon cancer between 2004 and 2007 from 4 datasets, including the SEER-Medicare Databases and the NCCN Outcomes Database, showed a survival benefit for adjuvant chemotherapy in this population (HR, 0.60; 95% CI, 0.53–0.68).[300] This study also looked specifically at the benefit of the addition of oxaliplatin to adjuvant therapy in these older stage III patients, and found only a small, non-significant benefit. Analysis of almost 12,000 patients from the ACCENT database also found a reduced benefit to the addition of oxaliplatin to fluoropyrimidines in the adjuvant setting in patients aged greater than or equal to 70 years.[305]

Subset analyses of major adjuvant therapy trials also show a lack of benefit to the addition of oxaliplatin in older patients. Subset analysis of the NSABP C-07 trial showed that the addition of oxaliplatin to 5-FU/LV gave no survival benefit in patients aged greater than or equal to 70 years with stage II or III colon cancer (n = 396), with a trend towards decreased survival (HR, 1.18; 95% CI, 0.86–1.62).[269] Similarly, in a subset analysis of the MOSAIC trial, 315 patients aged 70 to 75 years with stage II or III colon cancer derived no benefit from the addition of oxaliplatin (OS HR, 1.10; 95% CI, 0.73–1.65).[268]

However, a recent pooled analysis of individual patient data from the NSABP C-08, XELOXA, X-ACT, and AVANT trials found that DFS (HR, 0.77; 95% CI, 0.62–0.95; $P = .014$) and OS (HR, 0.78; 95% CI, 0.61–0.99; $P = .045$) were improved with adjuvant CapeOx or FOLFOX over 5-FU/LV in patients 70 years of age or older.[306]

As for the risks of adjuvant therapy in elderly patients, a pooled analysis of 37,568 patients from adjuvant trials in the ACCENT database found that the likelihood of early mortality after adjuvant treatment increased with age in a nonlinear fashion ($P < .001$).[307] For instance, the ORs for 30-day mortality for patients aged 70 years and aged 80 years compared to patients aged 60 years were 2.58 (95% CI, 1.88–3.54) and 8.61 (95% CI, 5.34–13.9), respectively. Patients aged 50 years, on the other hand, had a corresponding OR of 0.72 (95% CI, 0.47–1.10). However, the absolute risk of early mortality was very small, even for elderly patients (30-day mortality for 80-year-olds was 1.8%).

Overall, the benefit and toxicities of 5-FU/LV as adjuvant therapy seem to be similar in older and younger patients. However, the panel cautions that a benefit for the addition of oxaliplatin to 5-FU/LV in patients aged 70 years and older has not been proven in stage II or stage III colon cancer.

Timing of Adjuvant Therapy

A systematic review and meta-analysis of 10 studies involving more than 15,000 patients examined the effect of timing of adjuvant therapy after resection.[308] Results of this analysis showed that each 4-week delay in chemotherapy results in a 14% decrease in OS, indicating that adjuvant therapy should be administered as soon as the patient is medically able. These results are consistent with other similar analyses. In addition, a retrospective study of 7794 patients with stage II or III colon cancer from the National Cancer Data Base found that a delay of

>6 weeks between surgery and adjuvant therapy reduced survival after adjustment for clinical-, tumor-, and treatment-related factors.[309] Another retrospective study of 6620 patients with stage III colon cancer from the Netherlands Cancer Registry also found that starting adjuvant therapy after 8 weeks beyond resection was associated with worse survival.[310] However, some critics have pointed out that this type of analysis is biased by confounding factors such as comorbidities, which are likely to be higher in patients with a longer delay before initiation of chemotherapy.[311] In fact, the registry study found that patients who started therapy after 8 weeks were more likely to be older than 65 years, have had an emergency resection, and/or have a prolonged postoperative admission.[310]

Leucovorin Shortage

A shortage of LV recently existed in the United States. No specific data are available to guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levoleucovorin, which is commonly used in Europe. A dose of 200 mg/m^2 of levoleucovorin is equivalent to 400 mg/m^2 of standard LV. Another option is for practices or institutions to use lower doses of LV for all doses in all patients, because the panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that 175 mg of LV was associated with similar survival and 3-year recurrence rates as 25 mg of LV when given with bolus 5-FU as adjuvant therapy to patients after R0 resections for colorectal cancer.[312] Another study showed no difference in response rate or survival in patients with metastatic colorectal cancer receiving bolus 5-FU with either high-dose (500 mg/m^2) or low-dose (20 mg/m^2) LV.[313] Furthermore, the Mayo Clinic and North Central Cancer Treatment Group (NCCTG) determined that no therapeutic difference was seen between the use of high-dose (200 mg/m^2) or low-dose (20 mg/m^2) LV with bolus 5-FU in the treatment of advanced colorectal cancer, although the 5-FU doses were different in the treatment arms.[314] Finally, if none of the above options is available, treatment without LV would be reasonable. For patients who tolerate this without grade II or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered.

FOLFOX and Infusional 5-FU/LV

The European MOSAIC trial compared the efficacy of FOLFOX and 5-FU/LV in the adjuvant setting in 2246 patients with completely resected stage II and III colon cancer. Although this initial trial was performed with FOLFOX4, mFOLFOX6 has been the control arm for all recent and current National Cancer Institute (NCI) adjuvant studies for colorectal cancer, and the panel believes that mFOLFOX6 is the preferred FOLFOX regimen for adjuvant and metastatic treatments. Results of this study have been reported with median follow-ups up to 9.5 years.[245-247] For patients with stage III disease, DFS at 5 years was 58.9% in the 5-FU/LV arm and 66.4% in the FOLFOX arm (P = .005), and 10-year OS of patients with stage III disease receiving FOLFOX was statistically significantly increased compared with those receiving 5-FU/LV (67.1% vs. 59.0%; HR, 0.80; P = .016).[247] Although the incidence of grade 3 peripheral sensory neuropathy was 12.4% for patients receiving FOLFOX and only 0.2% for patients receiving 5-FU/LV, long-term safety results showed a gradual recovery for most of these patients. However, neuropathy was present in 15.4% of examined patients at 4 years (mostly grade 1), suggesting that oxaliplatin-induced neuropathy may not be completely reversible in some patients.[246]

An analysis of 5 observational data sources, including the SEER-Medicare and NCCN Outcomes Databases, showed that the addition of oxaliplatin to 5-FU/LV gave a survival advantage to the general stage III

colon cancer population treated in the community.[315] Another population-based analysis found that the harms of oxaliplatin in the medicare population with stage III colon cancer were reasonable, even in patients 75 years or older.[316] In addition, a pooled analysis of individual patient data from 4 randomized controlled trials revealed that the addition of oxaliplatin to capecitabine or 5-FU/LV improved outcomes in patients with stage III colon cancer.[317] Furthermore, analysis of data from 12,233 patients in the ACCENT database of adjuvant colon cancer trials support the benefit of oxaliplatin in patients with stage III disease.[318]

Based on the increases in DFS and OS with FOLFOX in the MOSAIC trial, FOLFOX (mFOLFOX6 preferred) is recommended as a preferred treatment for stage III colon cancer (category 1). Toxicity of this regimen is discussed in *Systemic Therapy for Advanced or Metastatic Disease*, below.

FLOX

A randomized phase III trial (NSABP C-07) compared the efficacy of FLOX with that of bolus 5-FU/LV in prolonging DFS in 2407 patients with stage II or III colon cancer.[250] Rates of 4-year DFS were 73.2% for FLOX and 67.0% for bolus 5-FU/LV, with an HR of 0.81 (95% CI, 0.69–0.94; *P* = .005) after adjustment for age and number of nodes, indicating a 19% reduction in relative risk.[250] A recent update of this study showed that the benefit of FLOX in DFS was maintained at 7-year median follow-up (*P* = .0017).[269] However, no statistically significant differences in OS (HR, 0.88; 95% CI, 0.76–1.03; *P* = .1173) or colon-cancer–specific mortality (HR, 0.88; 95% CI, 0.74–1.05; *P* = .1428) were observed when the arms were compared. Furthermore, survival after disease recurrence was significantly shorter in the group receiving oxaliplatin (HR, 1.20; 95% CI, 1.00–1.43; *P* = .0497).[269]

Grade-3 neurotoxicity, diarrhea, and dehydration were higher with FLOX than with 5-FU/LV,[269] and, when cross-study comparisons were made, the incidence of grade 3/4 diarrhea seemed to be considerably higher with FLOX than with FOLFOX. For example, rates of grade 3/4 diarrhea were 10.8% and 6.6% for patients receiving FOLFOX and infusional 5-FU/LV, respectively (*P* < .001), in the MOSAIC trial,[245] whereas 38% and 32% of patients were reported to have grade 3/4 diarrhea in the NSABP C-07 trial when receiving FLOX and bolus 5-FU/LV, respectively (*P* = .003).[250]

Capecitabine and CapeOx

Single-agent oral capecitabine as adjuvant therapy for patients with stage III colon cancer was shown to be at least equivalent to bolus 5-FU/LV (Mayo Clinic regimen) with respect to DFS and OS, with respective HRs of 0.87 (95% CI, 0.75–1.00; *P* < .001) and 0.84 (95% CI, 0.69–1.01; *P* = .07) in the X-ACT trial.[253] Final results of this trial were recently reported.[319] After a median follow-up of 6.9 years, the equivalencies in DFS and OS were maintained in all subgroups, including those 70 years of age or older.

Capecitabine was also assessed as adjuvant therapy for stage III colon cancer in combination with oxaliplatin (CapeOx) in the NO16968 trial and showed an improved 3-year DFS rate compared with bolus 5-FU/LV (66.5% vs. 70.9%).[251,252] Final results of this trial showed that OS at 7 years was improved in the CapeOx arm compared with the 5-FU/LV arm (73% vs. 67%; HR, 0.83; 95% CI, 0.70–0.99; *P* = .04).[320]

Another phase III trial compared CapeOx to mFOLFOX6 in 408 patients with stage III or high-risk stage II colon cancer.[321] No significant differences were seen in 3-year DFS and 3-year OS.

In addition, a pooled analysis of individual patient data from 4 randomized controlled trials revealed that the addition of oxaliplatin to capecitabine or 5-FU/LV improved outcomes in patients with stage III colon cancer.[317] Based on these data, CapeOx is listed in the guidelines with a category 1 designation as a preferred adjuvant therapy for patients with stage III colon cancer.

Regimens Not Recommended

Other adjuvant regimens studied for the treatment of early-stage colon cancer include 5-FU–based therapies incorporating irinotecan. The CALGB 89803 trial evaluated the IFL regimen versus 5-FU/LV alone in stage III colon cancer.[322] No improvement in either OS (*P* = .74) or DFS (*P* = .84) was observed for patients receiving IFL compared with those receiving 5-FU/LV. However, IFL was associated with a greater degree of neutropenia, neutropenic fever, and death.[322,323] Similar results were observed in a randomized phase III trial comparing bolus 5-FU/LV with the IFL regimen in stage II/III colon cancer.[324] In addition, FOLFIRI (infusional 5-FU/LV/irinotecan) has not been shown to be superior to 5-FU/LV in the adjuvant setting.[325,326] Thus, data do not support the use of irinotecan-containing regimens in the treatment of stage II or III colon cancer.

In the NSABP C-08 trial comparing 6 months of mFOLFOX6 with 6 months of mFOLFOX6 with bevacizumab plus an additional 6 months of bevacizumab alone in patients with stage II or III colon cancer, no statistically significant benefit in 3-year DFS was seen with the addition of bevacizumab (HR, 0.89; 95% CI, 0.76–1.04; *P* = .15).[327] Similar results were seen after a median follow-up of 5 years.[328] The results of the phase III AVANT trial evaluating bevacizumab in the adjuvant setting in a similar protocol also failed to show a benefit associated with bevacizumab in the adjuvant treatment of stage II or III colorectal cancer, and in fact showed a trend toward a detrimental effect to the addition of bevacizumab.[329] Furthermore, results of the open-label, randomized phase 3 QUASAR 2 trial showed that bevacizumab had no benefit in the adjuvant colorectal setting when added to capecitabine.[330] Therefore, bevacizumab has no role in the adjuvant treatment of stage II or III colon cancer.

The NCCTG Intergroup phase III trial N0147 assessed the addition of cetuximab to FOLFOX in the adjuvant treatment of stage III colon cancer. In patients with wild-type or mutant *KRAS*, cetuximab provided no added benefit and was associated with increases in grade 3/4 adverse events.[331] In addition, all subsets of patients treated with cetuximab experienced increases in grade 3/4 adverse events. The open-label, randomized, phase 3 PETACC-8 trial also compared FOLFOX with and without cetuximab.[332] Analysis of the wild-type *KRAS* exon 2 subset found that DFS was similar in both arms (HR, 0.99; 95% CI, 0.76–1.28), while adverse events (ie, rash, diarrhea, mucositis, infusion-related reactions) were more common in the cetuximab group. Therefore, cetuximab also has no role in the adjuvant treatment of colon cancer.

Perioperative Chemoradiation

Neoadjuvant or adjuvant radiation therapy delivered concurrently with 5-FU–based chemotherapy may be considered for very select patients with disease characterized as T4 tumors penetrating to a fixed structure or for patients with recurrent disease. Radiation therapy fields should include the tumor bed as defined by preoperative radiologic imaging and/or surgical clips. Intraoperative radiation therapy (IORT), if available, should be considered for these patients as an additional boost.[333,334] If IORT is not available, an additional 10 to 20 Gy of external beam radiation therapy (EBRT) and/or brachytherapy could be considered to a limited volume.

Chemoradiation can also be given to patients with locally unresectable disease or who are medically inoperable. In such cases, surgery with or without IORT can then be considered or additional lines of systemic therapy can be given.

If radiation therapy is to be used, conformal beam radiation should be the routine choice; intensity-modulated radiation therapy (IMRT), which uses computer imaging to focus radiation to the tumor site and potentially decrease toxicity to normal tissue,[335] should be reserved for unique clinical situations, such as unique anatomical situations or reirradiation of previously treated patients with recurrent disease.

Neoadjuvant Therapy for Resectable Colon Cancer

For the 2016 version of these guidelines, the panel added the option for neoadjuvant treatment with FOLFOX or CapeOx for patients with resectable, clinical T4b colon cancer. The randomized phase III FOxTROT trial is assessing whether this approach improves DFS (NCT00647530). Results from the feasibility phase of the trial were reported in 2012.[336] One hundred fifty patients with T3 (with ≥5 mm invasion beyond the muscularis propria) or T4 tumors were randomly assigned to 3 cycles of preoperative therapy (5-FU/LV/oxaliplatin), surgery, and 9 additional cycles of the same therapy or to surgery with 12 cycles of the same therapy given postoperatively. Preoperative therapy resulted in significant downstaging compared with postoperative therapy (P = .04), with acceptable toxicity.

Principles of the Management of Metastatic Disease

Approximately 50% to 60% of patients diagnosed with colorectal cancer develop colorectal metastases,[337-339] and 80% to 90% of these patients have unresectable metastatic liver disease.[338,340-343] Metastatic disease most frequently develops metachronously after treatment for locoregional colorectal cancer, with the liver being the most common site of involvement.[344] However, 20% to 34% of patients with colorectal cancer present with synchronous liver metastases.[343,345] Some evidence indicates that synchronous metastatic colorectal liver disease is associated with a more disseminated disease state and a worse prognosis than metastatic colorectal liver disease that develops metachronously. In a retrospective study of 155 patients who underwent hepatic resection for colorectal liver metastases, patients with synchronous liver metastases had more sites of liver involvement (P = .008) and more bilobar metastases (P = .016) than patients diagnosed with metachronous liver metastases.[346]

It has been estimated that more than half of patients who die of colorectal cancer have liver metastases at autopsy, with metastatic liver disease being the cause of death in most patients.[347] Reviews of autopsy reports of patients who died from colorectal cancer showed that the liver was the only site of metastatic disease in one-third of patients.[342] Furthermore, several studies have shown rates of 5-year survival to be low in patients with metastatic liver disease not undergoing surgery.[338,348] Certain clinicopathologic factors, such as the presence of extrahepatic metastases, the presence of >3 tumors, and a disease-free interval of less than 12 months, have been associated with a poor prognosis in patients with colorectal cancer.[345,349-353]

Other groups, including ESMO, have established guidelines for the treatment of metastatic colorectal cancer.[354] The NCCN recommendations are discussed below.

Surgical Management of Colorectal Metastases

Studies of selected patients undergoing surgery to remove colorectal liver metastases have shown that cure is possible in this population and should be the goal for a substantial number of these patients.[338,355]

Reports have shown 5-year DFS rates of approximately 20% in patients who have undergone resection of liver metastases,[350,353] and a recent meta-analysis reported a median 5-year survival of 38%.[356] In addition, retrospective analyses and meta-analyses have shown that patients with solitary liver metastases have a 5-year OS rate as high as 71% following resection.[357-359] Therefore, decisions relating to patient suitability, or potential suitability, and subsequent selection for metastatic colorectal surgery are critical junctures in the management of metastatic colorectal liver disease (discussed further in *Determining Resectability*).[360]

Colorectal metastatic disease sometimes occurs in the lung.[337] Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases.[201,361,362] Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in very highly selected cases.[363-367]

Evidence supporting resection of extrahepatic metastases in patients with metastatic colorectal cancer is limited. In a recent retrospective analysis of patients undergoing concurrent complete resection of hepatic and extrahepatic disease, the 5-year survival rate was lower than in patients without extrahepatic disease, and virtually all patients who underwent resection of extrahepatic metastases experienced disease recurrence.[368,369] However, a recent international analysis of 1629 patients with colorectal liver metastases showed that 16% of the 171 patients (10.4%) who underwent concurrent resection of extrahepatic and hepatic disease remained disease-free at a median follow-up of 26 months, suggesting that concurrent resection may be of significant benefit in well-selected patients (ie, those with a smaller total number of metastases).[367] A recent systematic review concluded similarly that carefully selected patients might benefit from this approach.[370]

Data suggest that a surgical approach to the treatment of recurrent hepatic disease isolated to the liver can be safely undertaken.[371-375] However, in a retrospective analysis, 5-year survival was shown to decrease with each subsequent curative-intent surgery, and the presence of extrahepatic disease at the time of surgery was independently associated with a poor prognosis.[372] In a more recent retrospective analysis of 43 patients who underwent repeat hepatectomy for recurrent disease, 5-year OS and PFS rates were reported to be 73% and 22%, respectively.[371] A recent meta-analysis of 27 studies including >7200 patients found that those with longer disease-free intervals; those whose recurrences were solitary, smaller, or unilobular; and those lacking extrahepatic disease derived more benefit from repeat hepatectomy.[376] Panel consensus is that re-resection of liver or lung metastases can be considered in carefully selected patients.[362,375,377]

Patients with a resectable primary colon tumor and resectable synchronous metastases can be treated with a staged or simultaneous resection, as discussed below in *Resectable Synchronous Liver or Lung Metastases*. For patients presenting with unresectable metastases and an intact primary that is not acutely obstructed, palliative resection of the primary is rarely indicated, and systemic chemotherapy is the preferred initial maneuver (discussed further in *Unresectable Synchronous Liver or Lung Metastases*).[378]

Local Therapies for Metastases

The standard of care for patients with resectable metastatic disease is surgical resection. If resection is not feasible, image-guided ablation[379-381] or stereotactic body radiation therapy (SBRT; also called stereotactic

ablative radiotherapy [SABR])[341,382,383] are reasonable options, as discussed in subsequent paragraphs. Many patients, however, are not surgical candidates and/or have disease that cannot be ablated with clear margins[381] or safely treated by SBRT. In select patients with liver-only or liver-dominant metastatic disease that cannot be resected or ablated arterially, other locally directed treatment options may be offered.[384-386]

A meta-analysis of 90 studies concluded that hepatic arterial infusion (HAI), radioembolization, and transcatheter arterial chemoembolization (TACE) have similar efficacy in patients with unresectable colorectal metastases in the liver.[387] Local therapies are described in more detail below. The role of non-extirpative local therapies in the treatment of colorectal metastases remains controversial.

Hepatic Arterial Infusion

Placement of a hepatic arterial port or implantable pump during surgical intervention for liver resection with subsequent infusion of chemotherapy directed to the liver metastases through the hepatic artery (ie, HAI) is an option (category 2B). In a randomized study of patients who had undergone hepatic resection, administration of floxuridine with dexamethasone through HAI and intravenous 5-FU with or without LV was shown to be superior to a similar systemic chemotherapy regimen alone with respect to 2-year survival free of hepatic disease.[342,388] The study was not powered for long-term survival, but a trend (not significant) was seen toward better long-term outcome in the group receiving HAI at later follow-up periods.[342,389] Several other clinical trials have shown significant improvement in response or time to hepatic disease progression when HAI therapy was compared with systemic chemotherapy, although most have not shown a survival benefit of HAI therapy.[342] Results of some studies also suggest that HAI may be useful in the conversion of patients from an unresectable to a resectable status.[390,391]

Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAI.[355] Limitations on the use of HAI therapy include the potential for biliary toxicity[342] and the requirement of specific technical expertise. Panel consensus is that HAI therapy should be considered selectively, and only at institutions with extensive experience in both the surgical and medical oncologic aspects of the procedure.

Arterially Directed Embolic Therapy

TACE involves hepatic artery catheterization to cause vessel occlusion with locally delivered chemotherapy.[385] A randomized trial using HAI to deliver drug-eluting beads loaded with irinotecan (DEBIRI) reported an OS benefit (22 months vs. 15 months; $P = .031$).[392] A 2013 meta-analysis identified 5 observational studies and 1 randomized trial and concluded that, although DEBIRI appears to be safe and effective for patients with unresectable colorectal liver metastases, additional trials are needed.[393] A more recent trial randomized 30 patients with colorectal liver metastases to FOLFOX/bevacizumab and 30 patients to FOLFOX/bevacizumab/DEBIRI.[394] DEBIRI resulted in an improvement in the primary outcome measure of response rate (78% vs. 54% at 2 months; $P = .02$).

Doxorubicin-eluting beads have also been studied; the strongest data supporting their effectiveness come from several phase II trials in hepatocellular carcinoma.[395-400] A recent systematic review concluded that data are not strong enough to recommend TACE for the treatment of colorectal liver metastases except as part of a clinical trial.[401]

The panel believes that arterially directed catheter therapy and, in particular, yttrium-90 microsphere selective internal radiation (see *Radioembolization*, below) is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.

Liver- or Lung-Directed Radiation

Local radiation therapies include arterial radioembolization with microspheres[402-412] and conformal (stereotactic) EBRT.[413]

EBRT to the metastatic site can be considered in highly selected cases in which the patient has a limited number of liver or lung metastases or the patient is symptomatic or in the setting of a clinical trial. It should be delivered in a highly conformal manner and should not be used in place of surgical resection. The possible techniques include three-dimensional conformal radiation therapy (CRT), SBRT,[341,382,383,414] and IMRT, which uses computer imaging to focus radiation to the tumor site and potentially decrease toxicity to normal tissue.[335,415-418]

Radioembolization

A prospective, randomized, phase III trial of 44 patients showed that radioembolization combined with chemotherapy can lengthen time to progression in patients with liver-limited metastatic colorectal cancer following progression on initial therapy (2.1 vs. 4.5 months; *P* = .03).[419] The effect on the primary endpoint of time to liver progression was more pronounced (2.1 vs. 5.5 months; *P* = .003). Treatment of liver metastases with yttrium-90 glass radioembolization in a prospective, multicenter, phase II study resulted in a median PFS of 2.9 months for patients with colorectal primaries who were refractory to standard treatment.[420] In the refractory setting, a CEA level ≥90 and lymphovascular invasion at the time of primary resection were negative prognostic factors for OS.[411] Several large case series have been reported for yttrium-90 radioembolization in patients with refractory unresectable colorectal liver metastases, and the technique appears to be safe with some clinical benefit.[404,421,422]

Results from the phase III randomized controlled SIRFLOX trial (yttrium-90 resin microspheres with FOLFOX+/- bevacizumab vs. FOLFOX+/- bevacizumab).[423] The trial assessed the safety and efficacy of yttrium-90 radioembolization as first-line therapy in 530 patients with colorectal liver metastases. Although the primary endpoint was not met, with PFS in the FOLFOX +/- bevacizumab arm at 10.2 months versus 10.7 months in the FOLFOX/Y-90 arm (HR, 0.93; 95% CI, 0.77–1.12; *P* = .43), a prolonged liver PFS was demonstrated for the study arm (20.5 months for the FOLFOX/Y90 arm vs. 12.6 months for the chemotherapy only arm; HR, 0.69; 95% CI, 0.55–0.90; *P* = .002).

Whereas very little data show any impact on patient survival and the data supporting its efficacy are limited, toxicity with radioembolization is relatively low.[423-426] Consensus amongst panel members is that arterially directed catheter therapy and, in particular, yttrium-90 microsphere selective internal radiation is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.

Tumor Ablation

Although resection is the standard approach for the local treatment of resectable metastatic disease, patients with liver or lung oligometastases can be considered for tumor ablation therapy.[427] Ablative techniques include radiofrequency ablation (RFA),[381,428] microwave ablation, cryoablation, percutaneous ethanol injection, and electro-coagulation. Evidence on the use of RFA as a reasonable treatment option for non-surgical candidates and those with recurrent disease after hepatectomy with small liver metastases that can be

treated with clear margins is growing.[381,428-431] Data on ablative techniques other than RFA are extremely limited.[432-438]

A small number of retrospective studies have compared RFA with resection in the treatment of liver or lung metastases.[358,439-442] Most of these studies have shown RFA to be inferior to resection in terms of rates of local recurrence and 5-year OS.[439,443] Whether the differences in outcome observed for patients with liver metastases treated with RFA versus resection alone are from patient selection bias, technologic limitations of RFA, or a combination of these factors is currently unclear.[441] A 2010 ASCO clinical evidence review determined that RFA has not been well-studied in the setting of colorectal cancer liver metastases, with no randomized controlled trials having been reported at that time.[438] The ASCO panel concluded that a compelling need exists for more research in this area. A 2012 Cochrane Database systematic review came to similar conclusions, as have separate meta-analyses.[436,437,444] Recently, a trial was reported in which 119 patients were randomized to systemic treatment or systemic treatment plus RFA with or without resection.[445] No difference in OS was seen, but PFS was improved at 3 years in the RFA group (27.6% vs. 10.6%; HR, 0.63; 95% CI, 0.42–0.95; *P* = .025). Similarly, 2 recent studies and a position paper by a panel of experts on ablation indicated that ablation may provide acceptable oncologic outcomes for selected patients with small liver metastases that can be ablated with sufficient margins.[379-381]

Resection or ablation (either alone or in combination with resection) should be reserved for patients with metastatic disease that is completely amenable to local therapy with adequate margins. Use of surgery, ablation, or the combination, with the goal of less-than-complete resection/ablation of all known sites of disease, is not recommended.

Peritoneal Carcinomatosis

Approximately 17% of patients with metastatic colorectal cancer have peritoneal carcinomatosis, with 2% having the peritoneum as the only site of metastasis. Patients with peritoneal metastases generally have a shorter PFS and OS than those without peritoneal involvement.[95] The goal of treatment for most abdominal/peritoneal metastases is palliative, rather than curative, and primarily consists of systemic therapy (see *Systemic Therapy for Advanced or Metastatic Disease*) with palliative surgery or stenting if needed for obstruction or impending obstruction.[446-448] If an R0 resection can be achieved, however, surgical resection of isolated peritoneal disease may be considered at experienced centers. The panel cautions that the use of bevacizumab in patients with colon or rectal stents is associated with a possible increased risk of bowel perforation.[449,450]

Cytoreductive Debulking with Hyperthermic Intraperitoneal Chemotherapy

Several surgical series and retrospective analyses have addressed the role of cytoreductive surgery (ie, peritoneal stripping surgery) in combination with perioperative hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis without extra-abdominal metastases.[451-459] In the only randomized controlled trial of this approach, Verwaal et al[460] randomized 105 patients to either standard therapy (5-FU/LV with or without palliative surgery) or to aggressive cytoreductive surgery and HIPEC with mitomycin C; postoperative 5-FU/LV was given to 33 of 47 patients. OS was 12.6 months in the standard arm and 22.3 months in the HIPEC arm (*P* = .032). However, treatment-related morbidity was high, and the mortality was 8% in the HIPEC group, mostly related to bowel leakage. In addition, long-term survival does not seem to be improved by this treatment as seen by follow-up results.[461] Importantly, this trial was

performed without oxaliplatin, irinotecan, or molecularly targeted agents. Some experts have argued that the OS difference seen might have been much smaller if these agents were used (ie, the control group would have had better outcomes).[462]

Other criticisms of the Verwaal trial have been published.[462] One important point is that the trial included patients with peritoneal carcinomatosis of appendiceal origin, a group that has seen greater benefit with the cytoreductive surgery/HIPEC approach.[452,456,463,464] A retrospective multicenter cohort study reported median OS times of 30 and 77 months for patients with peritoneal carcinomatosis of colorectal origin and appendiceal origin, respectively, treated with HIPEC or with cytoreductive surgery and early postoperative intraperitoneal chemotherapy.[456] The median OS time for patients with pseudomyxoma peritonei, which arises from mucinous appendiceal carcinomas, was not reached at the time of publication. A recent retrospective international registry study reported 10- and 15-year survival rates of 63% and 59%, respectively, in patients with pseudomyxoma peritonei from mucinous appendiceal carcinomas treated with cytoreductive surgery and HIPEC.[465] HIPEC was not shown to be associated with improvements in OS in this study, whereas completeness of cytoreduction was. Thus, for patients with pseudomyxoma peritonei, optimal treatment is still unclear.[466]

The individual components of the HIPEC approach have not been well studied. In fact, studies in rats have suggested that the hyperthermia component of the treatment is irrelevant.[467] Results of a retrospective cohort study also suggest that heat may not affect outcomes from the procedure.[453] In addition, a randomized trial compared systemic 5-FU/oxaliplatin to cytoreductive surgery and intraperitoneal 5-FU without heat.[468] Although terminated prematurely because of poor accrual, analysis suggested that the cytoreductive surgery plus IPEC approach may have been superior to the systemic therapy approach (2-year OS, 54% vs. 38%; *P* = .04) for patients with resectable colorectal peritoneal metastases.

In addition, significant morbidity and mortality are associated with this procedure. A 2006 meta-analysis of 2 randomized controlled trials and 12 other studies reported morbidity rates ranging from 23% to 44% and mortality rates ranging from 0% to 12%.[459] Furthermore, recurrences after the procedure are very common.[469] Whereas the risks are reportedly decreasing with time (ie, recent studies report 1%–5% mortality rates at centers of excellence[457,462]), the benefits of the approach have not been definitively shown, and HIPEC remains very controversial.[470-473]

The panel currently believes that complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for selected patients with limited peritoneal metastases for whom R0 resection can be achieved. The panel recognizes the need for randomized clinical trials that will address the risks and benefits associated with each of these modalities.

Determining Resectability

The consensus of the panel is that patients diagnosed with potentially resectable metastatic colorectal cancer should undergo an upfront evaluation by a multidisciplinary team, including surgical consultation (ie, with an experienced hepatic surgeon in cases involving liver metastases) to assess resectability status. The criteria for determining patient suitability for resection of metastatic disease are the likelihood of achieving complete resection of all evident disease with negative surgical margins and maintaining adequate liver reserve.[474-477] When the remnant liver is insufficient in size based on cross-sectional imaging volumetrics, preoperative portal vein embolization of the involved liver

can be performed to expand the future liver remnant.[478] It should be noted that size alone is rarely a contraindication to tumor resection. Resectability differs fundamentally from endpoints that focus more on palliative measures. Instead, the resectability endpoint is focused on the potential of surgery to cure the disease.[479] Resection should not be undertaken unless complete removal of all known tumor is realistically possible (R0 resection), because incomplete resection or debulking (R1/R2 resection) has not been shown to be beneficial.[339,474]

The role of PET/CT in determining resectability of patients with metastatic colorectal cancer is discussed in *Workup and Management of Synchronous Metastatic Disease*, below.

Conversion to Resectability

The majority of patients diagnosed with metastatic colorectal disease have unresectable disease. However, for those with liver-limited unresectable disease that, because of involvement of critical structures, cannot be resected unless regression is accomplished, chemotherapy is being increasingly considered in highly selected cases in an attempt to downsize colorectal metastases and convert them to a resectable status. Patients presenting with large numbers of metastatic sites within the liver or lung are unlikely to achieve an R0 resection simply on the basis of a favorable response to chemotherapy, as the probability of complete eradication of a metastatic deposit by chemotherapy alone is low. These patients should be regarded as having unresectable disease not amenable to conversion therapy. In some highly selected cases, however, patients with significant response to conversion chemotherapy can be converted from unresectable to resectable status.[443]

Any active metastatic chemotherapeutic regimen can be used in an attempt to convert an unresectable patient to a resectable status, because the goal is not specifically the eradication of micrometastatic disease, but rather the obtaining of optimal size regression of the visible metastases. An important point to keep in mind is that irinotecan- and oxaliplatin-based chemotherapeutic regimens may cause liver steatohepatitis and sinusoidal liver injury, respectively.[480-484] To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the patient becomes resectable. Some of the trials addressing various conversion therapy regimens are discussed below.

In the study of Pozzo et al, it was reported that chemotherapy with irinotecan combined with 5-FU/LV enabled a significant portion (32.5%) of the patients with initially unresectable liver metastases to undergo liver resection.[476] The median time to progression was 14.3 months, with all of these patients alive at a median follow-up of 19 months. In a phase II study conducted by the NCCTG,[340] 42 patients with unresectable liver metastases were treated with FOLFOX. Twenty-five patients (60%) had tumor reduction and 17 patients (40%; 68% of the responders) were able to undergo resection after a median period of 6 months of chemotherapy. In another study, 1104 patients with initially unresectable colorectal liver metastases were treated with chemotherapy, which included oxaliplatin in the majority of cases, and 138 patients (12.5%) classified as “good responders” underwent secondary hepatic resection.[349] The 5-year DFS rate for these 138 patients was 22%. In addition, results from a retrospective analysis of 795 previously untreated patients with metastatic colorectal cancer enrolled in the Intergroup N9741 randomized phase III trial evaluating the efficacy of mostly oxaliplatin-containing chemotherapy regimens indicated that 24 patients (3.3%; 2 of the 24 had lung metastases) were able to undergo curative resection after treatment.[485] The median OS time in this group was 42.4 months.

In addition, FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan) has been compared with FOLFIRI in 2 randomized clinical trials in patients with unresectable disease.[486,487] In both studies, FOLFOXIRI led to an increase in R0 secondary resection rates: 6% versus 15%, *P* = .033 in the Gruppo Oncologico Nord Ovest (GONO) trial[486]; and 4% versus 10%, *P* = .08 in the Gastrointestinal Committee of the Hellenic Oncology Research Group (HORG) trial.[487] In a follow-up study of the GONO trial, the 5-year survival rate was higher in the group receiving FOLFOXIRI (15% vs. 8%), with a median OS of 23.4 versus 16.7 months (*P* = .026).[488]

More recent favorable results of randomized clinical trials evaluating FOLFIRI or FOLFOX for the purpose of conversion of unresectable disease to resectable disease in combination with anti-epidermal growth factor receptor (EGFR) inhibitors have been reported.[489] For instance, in the CELIM phase II trial, patients were randomized to receive cetuximab with either FOLFOX6 or FOLFIRI.[489] Retrospective analysis showed that in both treatment arms combined resectability increased from 32% to 60% after chemotherapy in patients with wild-type *KRAS* exon 2 with the addition of cetuximab (*P* < .0001). Final analysis of this trial showed that the median OS of the entire cohort was 35.7 months (95% CI, 27.2–44.2 months), with no difference between the arms.[490] Another recent randomized controlled trial compared chemotherapy (mFOLFOX6 or FOLFIRI) plus cetuximab to chemotherapy alone in patients with unresectable colorectal cancer metastatic to the liver.[491] The primary endpoint was the rate of conversion to resectability based on evaluation by a multidisciplinary team. After evaluation, 20 of 70 (29%) patients in the cetuximab arm and 9 of 68 (13%) patients in the control arm were determined to be eligible for curative-intent hepatic resection. R0 resection rates were 25.7% in the cetuximab arm and 7.4% in the control arm (*P* < .01). In addition, surgery improved the median survival time compared to unresected participants in both arms, with longer survival in patients receiving cetuximab (46.4 vs. 25.7 months; *P* = .007 for the cetuximab arm and 36.0 vs. 19.6 months; *P* = .016 for the control arm). A recent meta-analysis of 4 randomized controlled trials concluded that the addition of cetuximab or panitumumab to chemotherapy significantly increased the response rate, the R0 resection rate (from 11%–18%; RR, 1.59; *P* = .04), and PFS, but not OS in patients with wild-type *KRAS* exon 2-containing tumors.[492]

The role of bevacizumab in the patient with unresectable disease, whose disease is felt to be potentially convertible to resectability with a reduction in tumor size, has also been studied. Data seem to suggest that bevacizumab modestly improves the response rate to irinotecan-based regimens.[493,494] Thus, when an irinotecan-based regimen is selected for an attempt to convert unresectable disease to resectability, the use of bevacizumab would seem to be an appropriate consideration. On the other hand, a 1400-patient, randomized, double-blind, placebo-controlled trial of CapeOx or FOLFOX with or without bevacizumab showed absolutely no benefit in terms of response rate or tumor regression for the addition of bevacizumab, as measured by both investigators and an independent radiology review committee.[495] Therefore, arguments for use of bevacizumab with oxaliplatin-based therapy in this “convert to resectability” setting are not compelling. However, because it is not known in advance whether resectability will be achieved, the use of bevacizumab with oxaliplatin-based therapy in this setting is acceptable.

When chemotherapy is planned for patients with initially unresectable disease, the panel recommends that a surgical re-evaluation be planned 2 months after initiation of chemotherapy, and that those patients who continue to receive chemotherapy undergo surgical re-

evaluation every 2 months thereafter.[484,496-498] Reported risks associated with chemotherapy include the potential for development of liver steatosis or steatohepatitis when oxaliplatin or irinotecan-containing chemotherapeutic regimens are administered.[480] To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the patient becomes resectable.

Neoadjuvant and Adjuvant Therapy for Resectable Metastatic Disease

The panel recommends that a course of an active systemic therapy regimen for metastatic disease, administered for a total perioperative treatment time of approximately 6 months, be considered for most patients undergoing liver or lung resection to increase the likelihood that residual microscopic disease will be eradicated (category 2B for the use of biologic agents in the perioperative metastatic setting). Although systemic therapy can be given before, between, or after resections, the total duration of perioperative systemic therapy should not exceed 6 months. A 2012 meta-analysis identified 3 randomized clinical trials comparing surgery alone to surgery plus systemic therapy with 642 evaluable patients with colorectal liver metastases.[499] The pooled analysis showed a benefit of chemotherapy in PFS (pooled HR, 0.75; CI, 0.62–0.91; *P* = .003) and DFS (pooled HR, 0.71; CI, 0.58–0.88; *P* = .001), but not in OS (pooled HR, 0.74; CI, 0.53–1.05; *P* = .088). Another meta-analysis published in 2015 combined data on 1896 patients from 10 studies and also found that perioperative chemotherapy improved DFS (HR, 0.81; 95% CI, 0.72–0.91; *P* = .0007) but not OS (HR, 0.88; 95% CI, 0.77–1.01; *P* = .07) in patients with resectable colorectal liver metastases.[500] Additional recent meta-analyses have also failed to observe an OS benefit with the addition of adjuvant chemotherapy in resectable metastatic colorectal cancer.[501,502]

The choice of chemotherapy regimen in the perioperative setting depends on several factors, including the chemotherapy history of the patient, whether disease is synchronous or metachronous, and the response rates and safety/toxicity issues associated with the regimens, as outlined in the guidelines. Biologics are not recommended in the perioperative metastatic setting, with the exception of initial therapy in unresectable patients who may be converted to a resectable state.

The optimal sequencing of systemic therapy and resection remains unclear. Patients with resectable disease may undergo resection first, followed by postoperative adjuvant chemotherapy. Alternatively, perioperative (neoadjuvant plus postoperative) systemic therapy can be used.[503,504]

Potential advantages of preoperative therapy include: earlier treatment of micrometastatic disease, determination of responsiveness to therapy (which can be prognostic and help in planning postoperative therapy), and avoidance of local therapy for those patients with early disease progression. Potential disadvantages include missing the “window of opportunity” for resection because of the possibility of disease progression or achievement of a complete response, thereby making it difficult to identify areas for resection.[342,505,506] In fact, results from recent studies of patients with colorectal cancer receiving preoperative therapy indicated that viable cancer was still present in most of the original sites of metastases when these sites were examined pathologically despite achievement of a complete response as evaluated on CT scan.[506-508] Therefore, during treatment with preoperative systemic therapy, frequent evaluations must be undertaken and close communication must be maintained among medical oncologists, radiologists, surgeons, and patients so that a treatment strategy can be developed that optimizes exposure to the preoperative regimen and facilitates an appropriately timed surgical intervention.[480]

Other reported risks associated with the preoperative therapy approach include the potential for development of liver steatohepatitis and sinusoidal liver injury when irinotecan- and oxaliplatin-based chemotherapeutic regimens are administered, respectively.[480-484] To reduce the development of hepatotoxicity, the neoadjuvant period is usually limited to 2 to 3 months, and patients should be carefully monitored by a multidisciplinary team.

Systemic Therapy for Advanced or Metastatic Disease

The current management of disseminated metastatic colon cancer involves various active drugs, either in combination or as single agents: 5-FU/LV, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, panitumumab, ziv-aflibercept, ramucirumab, regorafenib, trifluridine-tipiracil, pembrolizumab, and nivolumab.[255,313,486,487,495,509-545] The putative mechanisms of action of these agents are varied and include interference with DNA replication and inhibition of the activities of vascular endothelial growth factor (VEGF) and EGFRs.[546-549] The choice of therapy is based on consideration of the goals of therapy, the type and timing of prior therapy, the mutational profile of the tumor, and the differing toxicity profiles of the constituent drugs. Although the specific regimens listed in the guideline are designated according to whether they pertain to initial therapy, therapy after first progression, or therapy after second progression, it is important to clarify that these recommendations represent a continuum of care and that these lines of treatment are blurred rather than discrete.[525] For example, if oxaliplatin is administered as a part of an initial treatment regimen but is discontinued after 12 weeks or earlier for escalating neurotoxicity, continuation of the remainder of the treatment regimen would still be considered initial therapy.

Principles to consider at the start of therapy include preplanned strategies for altering therapy for patients exhibiting a tumor response or disease characterized as stable or progressive, and plans for adjusting therapy for patients who experience certain toxicities. For example, decisions related to therapeutic choices after first progression of disease should be based partly on the prior therapies received (ie, exposing the patient to a range of cytotoxic agents). Furthermore, an evaluation of the efficacy and safety of these regimens for an individual patient must take into account not only the component drugs, but also the doses, schedules, and methods of administration of these agents, and the potential for surgical cure and the performance status of the patient.

As initial therapy for metastatic disease in a patient appropriate for intensive therapy (ie, one with a good tolerance for this therapy for whom a high tumor response rate would be potentially beneficial), the panel recommends a choice of 5 chemotherapy regimens: FOLFOX (ie, mFOLFOX6),[533,550] FOLFIRI ,[255] CapeOx,[512,551,552] infusional 5-FU/LV or capecitabine,[255,313,536,545] or FOLFOXIRI,[486,487] with or without targeted agents.[553]

Sequencing and Timing of Therapies

Few studies have addressed the sequencing of therapies in advanced metastatic disease. Prior to the use of targeted agents, several studies randomized patients to different schedules.[550,554-556] The data from these trials suggest that there is little difference in clinical outcomes if intensive therapy is given in first line or if less intensive therapy is given first followed by more intensive combinations.

Results from a randomized study to evaluate the efficacy of FOLFIRI and FOLFOX regimens as initial therapy and to determine the effect of using sequential therapy with the alternate regimen after first

progression showed neither sequence to be significantly superior with respect to PFS or median OS.[550] A combined analysis of data from 7 recent phase III clinical trials in advanced colorectal cancer provided support for a correlation between an increase in median survival and administration of all of the 3 cytotoxic agents (ie, 5-FU/LV, oxaliplatin, irinotecan) at some point in the continuum of care.[557] Furthermore, OS was not found to be associated with the order in which these drugs were received.

A study of 6286 patients from 9 trials that evaluated the benefits and risks associated with intensive first-line treatment in the setting of metastatic colorectal cancer treatment according to patient performance status showed similar therapeutic efficacy for patients with performance status of 2 or 1 or less as compared with control groups, although the risks of certain gastrointestinal toxicities were significantly increased for patients with a performance status of 2.[558]

Overall, the panel does not consider one regimen (ie, FOLFOX, CapeOx, FOLFIRI, 5-FU/LV, capecitabine, FOLFOXIRI) to be preferable over the others as initial therapy for metastatic disease. The panel also does not indicate a preference for biologic agents used as part of initial therapy (ie, bevacizumab, cetuximab, panitumumab, none).

Maintenance Therapy

Interest in the use of a maintenance therapy approach after first-line treatment of unresectable, metastatic colorectal cancer is growing. In general, this approach involves intensive first-line therapy, followed by less intensive therapy until progression in patients with good response to initial treatment.

The CAIRO3 study was an open-label, phase III, multicenter randomized controlled trial assessing maintenance therapy with capecitabine/bevacizumab versus observation in 558 patients with metastatic colorectal cancer and with stable disease or better after first-line treatment with CapeOx/bevacizumab.[559] Following first progression, both groups were to receive CapeOx/bevacizumab again until second progression (PFS2). After a median follow-up of 48 months, the primary endpoint of PFS2 was significantly better in the maintenance arm (8.5 months vs. 11.7 months; HR, 0.67; 95% CI, 0.56–0.81; $P < .0001$), with 54% of patients overall receiving CapeOx/bevacizumab the second time. Quality of life was not affected by maintenance therapy, although 23% of patients in the maintenance group developed hand-foot syndrome during the maintenance period. A non-significant trend towards improved OS was seen in the maintenance arm (18.1 months vs. 21.6 months; adjusted HR, 0.83; 95% CI, 0.68–1.01; $P = .06$).

The AIO 0207 trial was an open-label, non-inferiority, randomized phase III trial that randomized 472 patients whose disease did not progress on induction FOLFOX/bevacizumab or CapeOx/bevacizumab to no maintenance therapy or to maintenance therapy with fluoropyrimidine/bevacizumab or with bevacizumab alone.[560] The planned protocol included re-introduction of primary therapy after first progression. The primary endpoint was time to failure of strategy, defined as time from randomization to second progression, death, and initiation of treatment with a new drug. After a medium follow-up of 17 months, the median time to failure of strategy was 6.4 months (95% CI, 4.8–7.6) for the no treatment group, 6.9 months (95% CI, 6.1–8.5) for the fluoropyrimidine/bevacizumab group, and 6.1 months (95% CI, 5.3–7.4) for the bevacizumab alone group. Compared with fluoropyrimidine/bevacizumab, bevacizumab alone was non-inferior, whereas the absence of maintenance therapy was not. However, only

about one third of trial participants received the re-induction therapy, thus limiting the interpretation of results. OS was one of the secondary endpoints of the trial, and no relevant difference was seen between the arms.

The randomized phase III non-inferiority SAKK 41/06 trial addressed the question of continuing bevacizumab alone as maintenance therapy after chemotherapy plus bevacizumab in first-line.[561] The primary endpoint of time to progression was not met (4.1 months for bevacizumab continuation vs. 2.9 months for no continuation; HR, 0.74; 95% CI, 0.58–0.96), and no difference in OS was observed (25.4 months vs. 23.8 months; HR, 0.83; 95% CI, 0.63–1.1; *P* = .2). Therefore, non-inferiority for treatment holidays versus bevacizumab maintenance therapy was not demonstrated.

The GERCOR DREAM trial (OPTIMOX3) was an international, open-label, phase III study that randomized patients with metastatic colorectal cancer without disease progression on bevacizumab-based therapy to maintenance therapy with bevacizumab or bevacizumab plus erlotinib.[562] Intention-to-treat analysis revealed an advantage in PFS (5.4 vs. 4.9 months; stratified HR, 0.81; 95% CI, 0.66–1.01; *P* = .06) and OS (24.9 vs. 22.1 months; stratified HR, 0.79; 95% CI, 0.63–0.99; *P* = .04) with combination therapy. A smaller randomized trial, however, showed no difference in PFS or OS between bevacizumab and bevacizumab/erlotinib maintenance therapy in patients with *KRAS* wild-type tumors.[563] A meta-analysis identified 3 randomized trials (682 patients) and concluded that maintenance therapy with bevacizumab/erlotinib significantly increases OS and PFS, with manageable toxicity.[564]

Another phase III trial investigated the role of capecitabine in the maintenance phase, after initial treatment with FOLFOX or CapeOx.[565] PFS, the primary endpoint, was 6.4 months in the capecitabine maintenance group and 3.4 months in the group that was observed until progression (HR, 0.54; 95% CI, 0.42–0.70; *P* < 0.001). A non-statistically significant difference in the median OS was also seen (HR 0.85; 95% CI, 0.64–1.11; *P* = .2247). Toxicities associated with the capecitabine maintenance therapy were acceptable.

Regimens Not Recommended

The consensus of the panel is that infusional 5-FU regimens seem to be less toxic than bolus regimens and that any bolus regimen of 5-FU is inappropriate when administered with either irinotecan or oxaliplatin. Therefore, the panel no longer recommends using the IFL regimen (which was shown to be associated with increased mortality and decreased efficacy relative to FOLFIRI in the BICC-C trial[493,566] and inferior to FOLFOX in the Intergroup trial[567]) at any point in the therapy continuum. 5-FU in combination with irinotecan or oxaliplatin should be administered via an infusional biweekly regimen,[255] or capecitabine can be used with oxaliplatin.[543]

The Dutch CAIRO trial showed promising results for the use of capecitabine/irinotecan (CapeIRI) in the first-line treatment of metastatic colorectal cancer.[555] However, in the American BICC-C trial, CapeIRI showed worse PFS than FOLFIRI (5.8 vs. 7.6 months; *P* = .015), and was considerably more toxic with higher rates of severe vomiting, diarrhea, and dehydration.[493] In this trial, the CapeIRI arm was discontinued. The EORTC study 40015 also compared FOLFIRI with CapeIRI and was discontinued after enrollment of only 85 patients because 7 deaths were determined to be treatment-related (5 in the CapeIRI arm).[568] Several European studies have assessed the safety and efficacy of CapeIRI in combination with bevacizumab (CapeIRI/Bev) in the first-line metastatic setting. A small Spanish study of 46 patients who received CapeIRI/Bev showed encouraging results

with good tolerability.[569] A similar trial by the Spanish group found similar results in 77 patients.[570] Preliminary results from a randomized phase II study conducted in France were presented in 2009, showing a manageable toxicity profile for CapeIRI/Bev in this setting.[571] Additionally, a randomized phase III HeCOG trial compared CapeIRI/Bev and FOLFIRI/Bev in the first-line metastatic setting and found no significant differences in efficacy between the regimens.[572] Despite the differing toxicity profiles reported, the toxicities seemed to be reasonable in both arms. Finally, a randomized phase II study of the AIO colorectal study group compared CapeOx plus bevacizumab with a modified CapeIRI regimen plus bevacizumab and found similar 6-month PFS and similar toxicities.[573] Because of the concerns about the toxicity of the CapeIRI combination, which may differ between American and European patients, the panel does not recommend CapeIRI or CapeIRI/Bev for the first-line treatment of metastatic colorectal cancer.

Other drug combinations that have produced negative results in phase III trials for the treatment of advanced colorectal cancer include sunitinib plus FOLFIRI, cetuximab plus brivanib, erlotinib plus bevacizumab, and cediranib plus FOLFOX/CapeOx.[574-577] These regimens are not recommended for the treatment of patients with colorectal cancer.

Results from 2 randomized phase III trials have shown that combination therapy with more than one biologic agent is not associated with improved outcomes and can cause increased toxicity.[538,578] In the PACCE trial, the addition of panitumumab to a regimen containing oxaliplatin- or irinotecan-based chemotherapy plus bevacizumab was associated with significantly shorter PFS and higher toxicity in both *KRAS* exon 2 wild-type and mutant gene groups.[578] Similar results were observed in the CAIRO2 trial with the addition of cetuximab to a regimen containing capecitabine, oxaliplatin, and bevacizumab.[538] Therefore, the panel strongly recommends against the use of therapy involving the concurrent combination of an anti-EGFR agent (cetuximab or panitumumab) and an anti-VEGF agent (bevacizumab).

FOLFOX

The phase III EORTC 40983 study, evaluating use of perioperative FOLFOX (6 cycles before and 6 cycles after surgery) for patients with resectable liver metastases, showed absolute improvements in 3-year PFS of 8.1% (P = .041) and 9.2% (P = .025) for all eligible patients and all resected patients, respectively, when chemotherapy in conjunction with surgery was compared with surgery alone.[579] The partial response rate after preoperative FOLFOX was 40%, and operative mortality was less than 1% in both treatment groups. However, no difference in OS was seen between the groups, perhaps because second-line therapy was given to 77% of the patients in the surgery-only arm and 59% of the patients in the chemotherapy arm.[580]

The addition of bevacizumab is an option when FOLFOX is chosen as initial therapy,[495,581] as is the addition of panitumumab or cetuximab for patients with disease characterized by wild-type *KRAS* exon 2 (see discussions on *Bevacizumab; Cetuximab and Panitumumab; The Role of KRAS, NRAS, and BRAF Status*; *The Role of Primary Tumor Sidedness;* and *Cetuximab or Panitumumab vs. Bevacizumab in First-Line*, below).[521,582,583] With respect to the treatment of metastatic disease with bevacizumab-containing regimens or chemotherapy without an additional biologic agent, panel consensus is that FOLFOX and CapeOx can be used interchangeably. Results from a recent registry-based cohort analysis of greater than 2000 patients support the equivalence of these combinations.[584]

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy.[585] Results of the OPTIMOX1 study showed that a “stop-and-go” approach using oxaliplatin-free intervals

resulted in decreased neurotoxicity but did not affect OS in patients receiving FOLFOX as initial therapy for metastatic disease.[586] Other trials have also addressed the question of treatment breaks, with or without maintenance therapy, and found that toxicity can be minimized with minimal or no effect on survival.[587] A recent meta-analysis of randomized controlled trials also concluded that intermittent delivery of systemic therapy does not compromise OS compared to continuous treatment.[588] Therefore, the panel recommends adjusting the schedule/timing of the administration of this drug as a means of limiting this adverse effect. Discontinuation of oxaliplatin from FOLFOX or CapeOx should be strongly considered after 3 months of therapy, or sooner for unacceptable neurotoxicity, with other drugs in the regimen maintained for the entire 6 months or until time of tumor progression. Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy until and unless they experience near-total resolution of that neurotoxicity.

In the phase II OPTIMOX2 trial, patients were randomized to receive either an OPTIMOX1 approach (discontinuation of oxaliplatin after 6 cycles of FOLFOX to prevent or reduce neurotoxicity with continuance of 5-FU/LV followed by reintroduction of oxaliplatin on disease progression) or an induction FOLFOX regimen (6 cycles) followed by discontinuation of all chemotherapy until tumor progression reached baseline, followed by reintroduction of FOLFOX.[589] Results of the study showed no difference in OS for patients receiving the OPTIMOX1 approach compared with those undergoing an early, pre-planned, chemotherapy-free interval (median OS 23.8 vs. 19.5 months; $P = .42$). However, the median duration of disease control, which was the primary endpoint of the study, reached statistical significance at 13.1 months in patients undergoing maintenance therapy and 9.2 months in patients with a chemotherapy-free interval ($P = .046$).[589]

The CONcePT trial also tested an intermittent oxaliplatin approach in patients with advanced colorectal cancer and found that it improved acute peripheral sensory neuropathy ($P = .037$) over continuous oxaliplatin.[590] The addition of oxaliplatin breaks also improved time to treatment failure (HR, 0.581; $P = .0026$) and time to tumor progression (HR, 0.533; $P = .047$).

Early data suggested that calcium/magnesium infusion might prevent oxaliplatin-related neurotoxicity.[591-598] However, the phase III randomized, double-blind N08CB study, which randomized 353 patients with colon cancer receiving adjuvant FOLFOX to calcium/magnesium infusion or placebo, found that calcium/magnesium did not reduce cumulative sensory neurotoxicity.[599] The panel therefore recommends against calcium/magnesium infusions for this purpose.

Severe Fluoropyrimidine-Associated Toxicity

Dihydropyrimidine dehydrogenase is the enzyme that catabolizes fluoropyrimidines.[600,601] Individuals with certain variants of the dihydropyrimidine dehydrogenase gene, *DPYD*, have a significantly elevated risk for severe, life-threatening toxicity after a standard dose of fluoropyrimidine because these variants result in a truncated protein and prolonged systemic exposure to fluoropyrimidine.[602-605] Pretreatment *DPYD* testing of all patients has the potential to identify the estimated 1% to 2% of the population with truncating alleles and an increased risk of severe toxicity.[606] These patients could be offered alternative regimens or receive dose reductions. In a prospective study, 22 patients with the *DPYD*2A* variant allele (of 2038 patients screened; 1.1%) were given a fluoropyrimidine dose reduction of 17% to 91% (median 48%).[607] Results showed a significant reduction in the risk of grade ≥3 toxicity compared with historic controls (28% vs. 73%; $P < .001$). None of the patients died from drug toxicity, compared with a 10% death rate

in the historical control group. This study also found the approach to be cost effective.

Universal pretreatment *DPYD* genotyping remains controversial, however, and the NCCN Panel does not support it at this time.

CapeOx

The combination of capecitabine and oxaliplatin, known as CapeOx or XELOX, has been studied as an active first-line therapy for patients with metastatic colorectal cancer.[512,551,552,608,609] In a randomized phase III trial comparing CapeOx and FOLFOX in 2034 patients, the regimens showed similar median PFS intervals of 8.0 and 8.5 months, respectively, and CapeOx was determined to be noninferior to FOLFOX as first-line treatment of metastatic disease.[512] Meta-analyses of randomized controlled trials also showed that CapeOx and FOLFOX had similar benefits for patients with metastatic colorectal cancer.[610,611]

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy (see *FOLFOX*, above).[612] Discontinuation of oxaliplatin from FOLFOX or CapeOx should be strongly considered after 3 months of therapy (the OPTIMOX1 approach[586]), or sooner for unacceptable neurotoxicity, with other drugs in the regimen maintained until tumor progression. A recent Turkish Oncology Group Trial showed that this stop-and-go approach is safe and effective in first-line with CapeOx/bevacizumab.[613] Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy until and unless they experience near-total resolution of that neurotoxicity. The panel recommends against the use of calcium/magnesium infusion to prevent oxaliplatin-related neurotoxicity.[599]

Regarding the toxicities associated with capecitabine use, the panel noted that: 1) patients with diminished creatinine clearance may accumulate levels of the drug, and therefore may require dose modification[614]; 2) the incidence of hand-foot syndrome was increased for patients receiving capecitabine-containing regimens versus either bolus or infusional regimens of 5-FU/LV[581,614]; and 3) North American patients may experience a higher incidence of adverse events with certain doses of capecitabine compared with patients from other countries.[615] These toxicities may necessitate modifications in the dosing of capecitabine[581,614,616] and patients on capecitabine should be monitored closely so that dose adjustments can be made at the earliest signs of certain side effects, such as hand-foot syndrome. Interestingly, a recent analysis of patients from the AIO's KRK-0104 trial and the Mannheim rectal cancer trial found that capecitabine-related hand-foot skin reactions were associated with an improved OS (75.8 vs. 41.0 months; P = .001; HR, 0.56).[617]

The addition of bevacizumab is an option if CapeOx is chosen as initial therapy.[495,581] With respect to the treatment of metastatic disease with bevacizumab-containing regimens or chemotherapy without an additional biologic agent, the consensus of the panel is that FOLFOX and CapeOx can be used interchangeably. Results from a recent registry-based cohort analysis of greater than 2000 patients support the equivalence of these combinations.[584]

FOLFIRI

Evidence for the comparable efficacy for FOLFOX and FOLFIRI comes from a crossover study in which patients received either FOLFOX or FOLFIRI as initial therapy and were then switched to the other regimen at disease progression.[550] Similar response rates and PFS times were obtained when these regimens were used as first-line therapy. Further support for this conclusion has come from results of a phase III trial

comparing the efficacy and toxicity of FOLFOX and FOLFIRI regimens in previously untreated patients with metastatic colorectal cancer.[514] No differences were observed in response rate, PFS times, and OS between the treatment arms.

Toxicities associated with irinotecan include both early and late forms of diarrhea, dehydration, and severe neutropenia.[618,619] Irinotecan is inactivated by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), which is also involved in converting substrates such as bilirubin into more soluble forms through conjugation with certain glycosyl groups. Deficiencies in UGT1A1 can be caused by certain genetic polymorphisms and can result in conditions associated with accumulation of unconjugated hyperbilirubinemias, such as types I and II of the Crigler-Najjar and Gilbert syndromes. Thus, irinotecan should be used with caution and at a decreased dose in patients with Gilbert syndrome or elevated serum bilirubin. Similarly, certain genetic polymorphisms in the gene encoding for UGT1A1 can result in a decreased level of glucuronidation of the active metabolite of irinotecan, resulting in an accumulation of the drug and increased risk for toxicity,[619-621] although severe irinotecan-related toxicity is not experienced by all patients with these polymorphisms.[621] Results from a dose-finding and pharmacokinetic study suggest that dosing of irinotecan should be individualized based on UGT1A1 genotype.[622] The maximum tolerated dose of intravenous irinotecan every 3 weeks was 850 mg, 700 mg, and 400 mg in patients with the *1/*1, *1/*/28, and *28/*28 genotypes, respectively.

Commercial tests are available to detect the UGT1A1*28 allele, which is associated with decreased gene expression and, hence, reduced levels of UGT1A1 expression. Also, a warning was added to the label for irinotecan indicating that a reduced starting dose of the drug should be used in patients known to be homozygous for UGT1A1*28.[618] A practical approach to the use of UGT1A1*28 allele testing with respect to patients receiving irinotecan has been presented,[621] although guidelines for use of this test in clinical practice have not been established. Furthermore, UGT1A1 testing on patients who experience irinotecan toxicity is not recommended, because they will require a dose reduction regardless of the UGT1A1 test result.

Results from a recent phase IV trial in 209 patients with metastatic colorectal cancer who received bevacizumab in combination with FOLFIRI as first-line therapy showed that this combination was as effective and well-tolerated as bevacizumab with other 5-FU-based therapies.[623] A phase III trial in Japan also showed that FOLFIRI plus bevacizumab is non-inferior to mFOLFOX6 plus bevacizumab with regard to PFS.[624] Therefore, the addition of bevacizumab to FOLFIRI is recommended as an option for initial therapy; alternatively, cetuximab or panitumumab (only for left-sided tumors characterized by wild-type *KRAS/NRAS*) can be added to this regimen (see discussions on *Bevacizumab; Cetuximab and Panitumumab*; *The Role of KRAS, NRAS, and BRAF Status; The Role of Primary Tumor Sidedness;* and *Cetuximab or Panitumumab vs. Bevacizumab in First-Line*, below).[521,532,535,541,625]

Infusional 5-FU/LV and Capecitabine

For patients with impaired tolerance to aggressive initial therapy, the guidelines recommend infusional 5-FU/LV or capecitabine with or without bevacizumab as an option.[255,529,530,540,543,581] Patients with metastatic cancer with no improvement in functional status after this less intensive initial therapy should receive best supportive care. Patients showing improvement in functional status should be treated with one of the options specified for initial therapy for advanced or metastatic disease. Toxicities associated with capecitabine use are discussed earlier (see *CapeOx*).

In a pooled analysis of results from 2 randomized clinical trials involving patients with a potentially curative resection of liver or lung metastases randomly assigned to either postoperative systemic chemotherapy with 5-FU/LV or observation alone after surgery, the median PFS was 27.9 months in the chemotherapy arm and 18.8 months for those undergoing surgery alone (HR, 1.32; 95% CI, 1.00–1.76; *P* = .058), with no significant difference in OS.[626]

Results were recently published from the open-label phase III AVEX trial, in which 280 patients aged 70 years or older were randomized to capecitabine with or without bevacizumab.[627] The trial met its primary endpoint, with the addition of bevacizumab giving a significantly improved median PFS (9.1 vs. 5.1 months; HR, 0.53; 95% CI, 0.41–0.69; *P* < .0001).

FOLFOXIRI

FOLFOXIRI is also listed as an option for initial therapy in patients with unresectable metastatic disease. Use of FOLFOXIRI compared with FOLFIRI as initial therapy for the treatment of metastatic disease has been investigated in 2 randomized phase III trials.[486,487] In a trial by the GONO group, statistically significant improvements in PFS (9.8 vs. 6.9 months; HR, 0.63; *P* = .0006) and median OS (22.6 vs. 16.7 months; HR, 0.70; *P* = .032) were observed in the FOLFOXIRI arm,[486] although no OS difference was seen between treatment arms in the HORG study (median OS was 19.5 and 21.5 months for FOLFIRI and FOLFOXIRI, respectively; *P* = .337).[487] Both studies showed some increased toxicity in the FOLFOXIRI arm (eg, significant increases in neurotoxicity and neutropenia,[486] diarrhea, alopecia, and neurotoxicity[487]), but no differences in the rate of toxic death were reported in either study. Long-term outcomes of the GONO trial with a median follow-up of 60.6 months were later reported.[488] The improvements in PFS and OS were maintained.

The panel includes the possibility of adding bevacizumab to FOLFOXIRI for initial therapy of patients with unresectable metastatic disease. Results of the GONO group's phase III TRIBE trial showed that FOLFOXIRI/bevacizumab significantly increased PFS (12.1 vs. 9.7 months; HR, 0.75; 95% CI, 0.62–0.90; *P* = .003) and response rate (65% vs. 53%; *P* = .006) compared to FOLFIRI/ bevacizumab in patients with unresectable metastatic colorectal cancer.[628] Subgroup analyses indicated that no benefit to the addition of oxaliplatin was seen in patients who received prior adjuvant therapy (64% of cases included oxaliplatin in the adjuvant regimen). Diarrhea, stomatitis, neurotoxicity, and neutropenia were significantly more prevalent in the FOLFOXIRI arm. In an updated analysis on the TRIBE trial, investigators reported the median OS at 29.8 months (95% CI, 26.0–34.3) in the FOLFOXIRI plus bevacizumab arm and 25.8 months (95% CI, 22.5–29.1) in the FOLFIRI plus bevacizumab arm (HR, 0.80; 95% CI, 0.65–0.98; *P* = .03).[629]

Results from the randomized phase II OLIVIA trial, which compared mFOLFOX6/bevacizumab to FOLFOXIRI/bevacizumab in patients with unresectable colorectal liver metastases, were also reported.[630] Improvement in R0 resection rate was seen in the FOLFOXIRI/bevacizumab arm (49% vs. 23%; 95% CI, 4%–48%) and in the primary endpoint of overall (R0/R1/R2) resection rate (61% vs. 49%; 95% CI, −11%–36%).

Bevacizumab

Bevacizumab is a humanized monoclonal antibody that blocks the activity of VEGF, a factor that plays an important role in tumor angiogenesis.[631] Pooled results from several randomized phase II studies have shown that the addition of bevacizumab to first-line 5-FU/LV improved OS in patients with unresectable metastatic colorectal cancer compared with those receiving these regimens without

bevacizumab.[494,632,633] A combined analysis of the results of these trials showed that the addition of bevacizumab to 5-FU/LV was associated with a median survival of 17.9 versus 14.6 months for regimens consisting of 5-FU/LV or 5-FU/LV plus irinotecan without bevacizumab (P = .008).[530] A study of previously untreated patients receiving bevacizumab plus IFL also provided support for the inclusion of bevacizumab in initial therapy.[494] In that pivotal trial, a longer survival time was observed with the use of bevacizumab (20.3 vs. 15.6 months; HR, 0.66; P < .001).

Results have also been reported from a large, head-to-head, randomized, double-blind, placebo-controlled, phase III study (NO16966) in which CapeOx (capecitabine dose, 1000 mg/m^2, twice daily for 14 days) with bevacizumab or placebo was compared with FOLFOX with bevacizumab or placebo in 1400 patients with unresectable metastatic disease.[495] The addition of bevacizumab to oxaliplatin-based regimens was associated with a more modest increase of 1.4 months in PFS compared with these regimens without bevacizumab (HR, 0.83; 97.5% CI, 0.72–0.95; P = .0023), and the difference in OS, which was also a modest 1.4 months, did not reach statistical significance (HR, 0.89; 97.5% CI, 0.76–1.03; P = .077).[495] Researchers have suggested that differences observed in cross-study comparisons of NO16966 with other trials might be related to differences in the discontinuation rates and durations of treatment between trials, although these hypotheses are conjectural.[495] However, in this 1400-patient randomized study, absolutely no difference in response rate was seen with and without bevacizumab, and this finding could not have been influenced by the early withdrawal rates, which would have occurred after the responses would have occurred. Results of subset analyses evaluating the benefit of adding bevacizumab to either FOLFOX or CapeOx indicated that bevacizumab was associated with improvements in PFS when added to CapeOx but not FOLFOX.[495]

The combination of FOLFIRI and bevacizumab in the first-line treatment of advanced colorectal cancer has been studied, although no randomized controlled trials have compared FOLFIRI with and without bevacizumab. A recent systematic review with a pooled analysis (29 prospective and retrospective studies, 3502 patients) found that the combination gave a response rate of 51.4%, a median PFS of 10.8 months (95% CI, 8.9–12.8), and a median OS of 23.7 months (95% CI, 18.1–31.6).[634] FOLFOXIRI with bevacizumab is also an accepted combination (see *FOLFOXIRI*, above), although no randomized controlled trials have compared FOLFOXIRI with and without bevacizumab.

A prospective observational cohort study (ARIES) included 1550 patients who received first-line therapy with bevacizumab with chemotherapy for metastatic colorectal cancer and 482 patients treated with bevacizumab in second-line.[635] Median OS was 23.2 months (95% CI, 21.2–24.8) for the first-line cohort and 17.8 months (95% CI, 16.5–20.7) in the second-line group. A similar cohort study (ETNA) of first-line bevacizumab use with irinotecan-based therapy reported a median OS of 25.3 months (95% CI, 23.3–27.0).[636]

Several meta-analyses have shown a benefit for the use of bevacizumab in first-line therapy for metastatic colorectal cancer.[637-645] A meta-analysis of 6 randomized clinical trials (3060 patients) that assessed the efficacy of bevacizumab in first-line treatment of metastatic colorectal cancer found that bevacizumab gave a PFS (HR, 0.72; 95% CI, 0.66–0.78; P < .00001) and OS (HR, 0.84; 95% CI, 0.77–0.91; P < .00001) advantage.[646] However, subgroup analyses showed that the advantage was limited to irinotecan-based regimens. In

addition, a recent analysis of the SEER-Medicare database found that bevacizumab added a modest improvement to OS of patients with stage IV colorectal cancer diagnosed between 2002 and 2007 (HR, 0.85; 95% CI, 0.78–0.93).[647] The survival advantage was not evident when bevacizumab was combined with oxaliplatin-based chemotherapy, but was evident in irinotecan-based regimens. Limitations of this analysis have been discussed,[648,649] but, overall, the addition of bevacizumab to first-line chemotherapy appears to offer a modest clinical benefit.

No data directly address whether bevacizumab should be used with chemotherapy in the perioperative treatment of resectable metastatic disease. Recent data regarding the lack of efficacy of bevacizumab in the adjuvant setting in stage II and III colon cancer[327,329] have prompted some to reconsider the role of bevacizumab in the adjuvant setting of resectable colorectal metastases. However, the panel does not recommend the use of bevacizumab in the perioperative stage IV setting.

A recent meta-analysis of randomized controlled trials showed that the addition of bevacizumab to chemotherapy is associated with a higher incidence of treatment-related mortality than chemotherapy alone (RR, 1.33; 95% CI, 1.02–1.73; *P* = .04), with hemorrhage (23.5%), neutropenia (12.2%), and gastrointestinal perforation (7.1%) being the most common causes of fatality.[650] Venous thromboembolisms, on the other hand, were not increased in patients receiving bevacizumab with chemotherapy versus those receiving chemotherapy alone.[651] Another meta-analysis showed that bevacizumab was associated with a significantly higher risk of hypertension, gastrointestinal hemorrhage, and perforation, although the overall risk for hemorrhage and perforation is quite low.[652] The risk of stroke and other arterial events is increased in patients receiving bevacizumab, especially in those aged 65 years or older. Gastrointestinal perforation is a rare but important side effect of bevacizumab therapy in patients with colorectal cancer.[581,653] Extensive prior intra-abdominal surgery, such as peritoneal stripping, may predispose patients to gastrointestinal perforation. A small cohort of patients with advanced ovarian cancer had an unacceptably high rate of gastrointestinal perforation when treated with bevacizumab.[654] This result illustrated that peritoneal debulking surgery may be a risk factor for gastrointestinal perforation, whereas the presence of an intact primary tumor does not seem to increase the risk for gastrointestinal perforation. The FDA recently approved a safety label warning of the risk for necrotizing fasciitis, sometimes fatal and usually secondary to wound healing complications, gastrointestinal perforation, or fistula formation after bevacizumab use.[631]

Use of bevacizumab may interfere with wound healing.[581,631,653] A retrospective evaluation of data from 2 randomized trials of 1132 patients undergoing chemotherapy with or without bevacizumab as initial therapy for metastatic colorectal cancer indicated that the incidence of wound healing complications was increased for the group of patients undergoing a major surgical procedure while receiving a bevacizumab-containing regimen compared with the group receiving chemotherapy alone while undergoing major surgery (13% vs. 3.4%, respectively; *P* = .28).[653] However, when chemotherapy plus bevacizumab or chemotherapy alone was administered before surgery, with a delay between bevacizumab administration and surgery of at least 6 weeks, the incidence of wound healing complications in either group of patients was low (1.3% vs. 0.5%; *P* = .63). Similarly, results of a single-center, nonrandomized phase II trial of patients with potentially resectable liver metastases showed no increase in bleeding or wound complications when the bevacizumab component of CapeOx plus bevacizumab therapy was stopped 5 weeks before surgery (ie, bevacizumab excluded from the sixth cycle of therapy).[655] In addition, no

significant differences in bleeding, wound, or hepatic complications were seen in a retrospective trial evaluating the effects of preoperative bevacizumab stopped at 8 weeks or less versus at more than 8 weeks before resection of liver colorectal metastases in patients receiving oxaliplatin- or irinotecan-containing regimens.[656] The panel recommends an interval of at least 6 weeks (which corresponds to 2 half-lives of the drug[631]) between the last dose of bevacizumab and any elective surgery.

Preclinical studies suggested that cessation of anti-VEGF therapy might be associated with accelerated recurrence, more aggressive tumors on recurrence, and increased mortality. A recent retrospective meta-analysis of 5 placebo-controlled, randomized phase III trials including 4205 patients with metastatic colorectal, breast, renal, or pancreatic cancer found no difference in time to disease progression and mortality with discontinuation of bevacizumab versus discontinuation of placebo.[657] Although this meta-analysis has been criticized,[658,659] the results are supported by recent results from the NSABP Protocol C-08 trial.[327] This trial included patients with stage II and stage III colorectal cancer, and no differences in recurrence, mortality, or mortality 2 years after recurrence were seen between patients receiving bevacizumab versus patients in the control arm. These results suggest that no "rebound effect" is associated with bevacizumab use.

Cetuximab and Panitumumab

Cetuximab and panitumumab are monoclonal antibodies directed against EGFR that inhibit its downstream signaling pathways. Panitumumab is a fully human monoclonal antibody, whereas cetuximab is a chimeric monoclonal antibody.[660,661] Cetuximab and panitumumab have been studied in combination with FOLFIRI and FOLFOX as initial therapy options for treatment of metastatic colorectal cancer. Recent meta-analyses of randomized controlled trials have concluded that EGFR inhibitors provide a clear clinical benefit in the treatment in patients with *RAS* wild-type metastatic colorectal cancer.[662,663] Individual trials and the role of *KRAS, NRAS,* and *BRAF* are discussed below.

Administration of either cetuximab or panitumumab has been associated with severe infusion reactions, including anaphylaxis, in 3% and 1% of patients, respectively.[660,661] Based on case reports and a small trial, administration of panitumumab seems to be feasible for patients experiencing severe infusion reactions to cetuximab.[664-666] Skin toxicity is a side effect of both of these agents and is not considered part of the infusion reactions. The incidence and severity of skin reactions with cetuximab and panitumumab seem to be very similar. Furthermore, the presence and severity of skin rash in patients receiving either of these drugs have been shown to predict increased response and survival.[541,667-671] A recent NCCN task force addressed the management of dermatologic and other toxicities associated with anti-EGFR inhibitors.[672] Cetuximab and panitumumab have also been associated with a risk for venous thromboembolic and other serious adverse events.[673,674]

Based on the results of the PACCE and CAIRO2 trials, the panel strongly advises against the concurrent use of bevacizumab with either cetuximab or panitumumab (see *Bevacizumab*, above).[538,578] Several trials that assessed EGFR inhibitors in combination with various chemotherapy agents are discussed below.

The Role of Primary Tumor Sidedness

A growing body of data has shown that the location of the primary tumor can be both prognostic and predictive of response to EGFR inhibitors in metastatic colorectal cancer.[675-682] For example, outcomes of 75 patients with metastatic colorectal cancer treated with cetuximab, panitumumab,

or cetuximab/irinotecan in first-line or subsequent lines of therapy at 3 Italian centers were analyzed based on sidedness of the primary tumor.[676] No responses were seen in the patients with right-sided primary tumors compared with a response rate of 41% in those with left-sided primaries (*P* = .003). The median PFS was 2.3 and 6.6 months in patients with right-sided and left-sided tumors, respectively (HR, 3.97; 95% CI, 2.09–7.53; *P* < .0001).

The strongest evidence for the predictive value of primary tumor sidedness and response to EGFR inhibitors is in the first-line treatment of patients in the phase III CALGB/SWOG 80405 trial.[682,683] The study showed that patients with all *RAS* wild-type, right-sided primary tumors (cecum to hepatic flexure) had longer OS if treated with bevacizumab than if treated with cetuximab in first line (HR, 1.36; 95% CI, 0.93–1.99; *P* = .10), whereas patients with all *RAS* wild-type, left-sided primary tumors (splenic flexure to rectum) had longer OS if treated with cetuximab than if treated with bevacizumab (HR, 0.77; 95% CI, 0.59–0.99; *P* = 0.04).[683] OS was prolonged with cetuximab versus bevacizumab in the left-sided primary group (39.3 months vs. 32.6 months) but shortened in the right-sided primary group (13.6 months vs. 29.2 months).

These and other data suggest that cetuximab and panitumumab confer little if any benefit to patients with metastatic colorectal cancer if the primary tumor originated on the right side.[675,676,678,679] The panel believes that primary tumor sidedness is a surrogate for the non-random distribution of molecular subtypes across the colon and that the on-going analysis of tumor specimens from the study will enable a better understanding of the biologic explanation of the observed difference in response to EGFR inhibitors. Until that time, only patients whose primary tumors originated on the left side of the colon (splenic flexure to rectum) should be offered cetuximab or panitumumab in the first-line treatment of metastatic disease. Evidence also suggests that sidedness is predictive of response to EGFR inhibitors in subsequent lines of therapy,[675,676,679] but the panel awaits more definitive studies. Until such data are available, all patients with *RAS* wild-type tumors can be considered for panitumumab or cetuximab in subsequent lines of therapy if neither was previously given.

The Role of KRAS, NRAS, and BRAF Status

The receptor for EGFR has been reported to be overexpressed in 49% to 82% of colorectal tumors.[684-687] EGFR testing of colorectal tumor cells has no proven predictive value in determining likelihood of response to either cetuximab or panitumumab. Data from the BOND study indicated that the intensity of immunohistochemical staining of EGFR in colorectal tumor cells did not correlate with the response rate to cetuximab.[515] A similar conclusion was drawn with respect to panitumumab.[688] Therefore, routine EGFR testing is not recommended, and no patient should be considered for or excluded from cetuximab or panitumumab therapy based on EGFR test results.

Cetuximab and panitumumab are monoclonal antibodies directed against EGFR that inhibit its downstream signaling pathways, but EGFR status as assessed using IHC is not predictive of treatment efficacy.[515,689] Furthermore, cetuximab and panitumumab are only effective in approximately 10% to 20% of patients with colorectal cancer.[515,542,689] The RAS/RAF/MAPK pathway is downstream of EGFR; mutations in components of this pathway are being studied in search of predictive markers for efficacy of these therapies.

A sizable body of literature has shown that tumors with a mutation in codon 12 or 13 of exon 2 of the *KRAS* gene are essentially insensitive to cetuximab or panitumumab therapy (see *KRAS Exon 2 Mutations*, below).[509,541,582,668,690-694] More recent evidence shows mutations in *KRAS*

outside of exon 2 and mutations in *NRAS* are also predictive for a lack of benefit to cetuximab and panitumumab (see *NRAS and Other KRAS Mutations, below*).[663,695]

The panel therefore strongly recommends *KRAS/NRAS* genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer. Patients with known *KRAS* or *NRAS* mutations should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, because they have virtually no chance of benefit and the exposure to toxicity and expense cannot be justified. It is implied throughout the guidelines that NCCN recommendations involving cetuximab or panitumumab relate only to patients with disease characterized by *KRAS/NRAS* wild-type genes. ASCO released a Provisional Clinical Opinion Update on extended *RAS* testing in patients with metastatic colorectal cancer that is consistent with the NCCN panel's recommendations.[696]

The panel strongly recommends genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer for *RAS* (*KRAS* exon 2 and non-exon 2; *NRAS*) and *BRAF at diagnosis of stage IV disease*. The recommendation for *KRAS/NRAS* testing, at this point, is not meant to indicate a preference regarding regimen selection in the first-line setting. Rather, this early establishment of *KRAS/NRAS* status is appropriate to plan for the treatment continuum, so that the information may be obtained in a non-time–sensitive manner and the patient and provider can discuss the implications of a *KRAS/NRAS* mutation, if present, while other treatment options still exist. Note that because anti-EGFR agents have no role in the management of stage I, II, or III disease, *KRAS/NRAS* genotyping of colorectal cancers at these earlier stages is not recommended.

KRAS mutations are early events in colorectal cancer formation, and therefore a very tight correlation exists between mutation status in the primary tumor and the metastases.[697-699] For this reason, *KRAS/NRAS* genotyping can be performed on archived specimens of either the primary tumor or a metastasis. Fresh biopsies should not be obtained solely for the purpose of *KRAS/NRAS* genotyping unless an archived specimen from either the primary tumor or a metastasis is unavailable.

The panel recommends that *KRAS, NRAS, and BRAF* gene testing be performed only in laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing.[700] No specific testing methodology is recommended.[701]

***KRAS* Exon 2 Mutations:** Approximately 40% of colorectal cancers are characterized by mutations in codons 12 and 13 in exon 2 of the coding region of the *KRAS* gene.[282,509] A sizable body of literature has shown that these *KRAS* exon 2 mutations are predictive of lack of response to cetuximab or panitumumab therapy,[509,541,582,668,690-694,702] and FDA labels for cetuximab and panitumumab specifically state that these agents are not recommended for the treatment of colorectal cancer characterized by these mutations.[660,661] Results are mixed as far as the prognostic value of *KRAS* mutations. In the Alliance N0147 trial, patients with *KRAS* exon 2 mutations experienced a shorter DFS than patients without such mutations.[703] At this time, however, the test is not recommended for prognostic reasons.

A retrospective study from De Roock et al[704] raised the possibility that codon 13 mutations (G13D) in *KRAS* may not be absolutely predictive of non-response. Another retrospective study showed similar results.[694] However, more recent retrospective analysis of 3 randomized controlled phase III trials concluded that patients with *KRAS* G13D mutations were

unlikely to respond to panitumumab.[705] Results from a prospective phase II single-arm trial assessed the benefit of cetuximab monotherapy in 12 patients with refractory metastatic colorectal cancer whose tumors contained *KRAS* G13D mutations.[706] The primary endpoint of 4-month progression-free rate was not met (25%), and no responses were seen. Preliminary results of the AGITG phase II ICE CREAM trial also failed to see a benefit of cetuximab monotherapy in patients with *KRAS* G13D mutations.[707] However, partial responses were reported after treatment with irinotecan plus cetuximab in 9% of this irinotecan-refractory population. The panel believes that patients with any known *KRAS* mutation, including G13D, should not be treated with cetuximab or panitumumab.

***NRAS* and Other *KRAS* Mutations:** In the AGITG MAX study, 10% of patients with wild-type *KRAS* exon 2 had mutations in *KRAS* exons 3 or 4 or in *NRAS* exons 2, 3, and 4.[708] In the PRIME trial, 17% of 641 patients without *KRAS* exon 2 mutations were found to have mutations in exons 3 and 4 of *KRAS* or mutations in exons 2, 3, and 4 of *NRAS*. A predefined retrospective subset analysis of data from PRIME revealed that PFS (HR, 1.31; 95% CI, 1.07–1.60; *P* = .008) and OS (HR, 1.21; 95% CI, 1.01–1.45; *P* = .04) were decreased in patients with any *KRAS* or *NRAS* mutation who received panitumumab plus FOLFOX compared to those who received FOLFOX alone.[695] These results show that panitumumab does not benefit patients with *KRAS* or *NRAS* mutations and may even have a detrimental effect in these patients.

Updated analysis of the FIRE-3 trial (discussed in *Cetuximab or Panitumumab vs. Bevacizumab in First-Line,* below) was recently published.[709] When all *RAS* (*KRAS/NRAS*) mutations were considered, PFS was significantly worse in patients with *RAS*-mutant tumors receiving FOLFIRI plus cetuximab than in patients with *RAS*-mutant tumors receiving FOLFIRI plus bevacizumab (6.1 months vs. 12.2 months; *P* = .004). On the other hand, patients with *KRAS/NRAS* wild-type tumors showed no difference in PFS between the regimens (10.4 months vs. 10.2 months; *P* = .54). This result indicates that cetuximab likely has a detrimental effect in patients with *KRAS* or *NRAS* mutations.

The FDA indication for panitumumab was recently updated to state that panitumumab is not indicated for the treatment of patients with *KRAS* or *NRAS* mutation-positive disease in combination with oxaliplatin-based chemotherapy.[661] The NCCN Colon/Rectal Cancer Panel believes that non-exon 2 *KRAS* mutation status and *NRAS* mutation status should be determined at diagnosis of stage IV disease. Patients with any known *KRAS* mutation (exon 2 or non-exon 2) or *NRAS* mutation should not be treated with either cetuximab or panitumumab.

***BRAF* V600E Mutations:** Although mutations of *KRAS/NRAS* indicate a lack of response to EGFR inhibitors, many tumors containing wild-type *KRAS/NRAS* still do not respond to these therapies. Therefore, studies have addressed factors downstream of *KRAS/NRAS* as possible additional biomarkers predictive of response to cetuximab or panitumumab. Approximately 5% to 9% of colorectal cancers are characterized by a specific mutation in the *BRAF* gene (V600E).[625,710] *BRAF* mutations are, for all practical purposes, limited to tumors that do not have *KRAS* exon 2 mutations.[710,711] Activation of the protein product of the non-mutated *BRAF* gene occurs downstream of the activated KRAS protein in the EGFR pathway; the mutated *BRAF* protein product is believed to be constitutively active,[712-714] thereby putatively bypassing inhibition of EGFR by cetuximab or panitumumab.

Limited data from unplanned retrospective subset analyses of patients with metastatic colorectal cancer treated in the first-line setting suggest that although a *BRAF* V600E mutation confers a poor prognosis regardless of treatment, patients with disease characterized by this

mutation may receive some benefit from the addition of cetuximab to front-line therapy.[625,715] A planned subset analysis of the PRIME trial also found that mutations in *BRAF* indicated a poor prognosis but were not predictive of benefit to panitumumab added to FOLFOX in first-line treatment of metastatic colorectal cancer.[695] On the other hand, results from the randomized phase III Medical Research Council (MRC) COIN trial suggest that cetuximab may have no effect or even a detrimental one in patients with *BRAF*-mutated tumors treated with CapeOx or FOLFOX in the first-line setting.[711]

In subsequent lines of therapy, retrospective evidence suggests that mutated *BRAF* is a marker of resistance to anti-EGFR therapy in the non-first-line setting of metastatic disease.[716-718] A retrospective study of 773 primary tumor samples from patients with chemotherapy-refractory disease showed that *BRAF* mutations conferred a significantly lower response rate to cetuximab (2/24; 8.3%) compared with tumors with wild-type *BRAF* (124/326; 38.0%; *P* = .0012).[719] Furthermore, data from the multicenter randomized controlled PICCOLO trial are consistent with this conclusion, with a suggestion of harm seen for the addition of panitumumab to irinotecan in the non-first-line setting in the small subset of patients with *BRAF* mutations.[720]

A meta-analysis published in 2015 identified 9 phase III trials and 1 phase II trial that compared cetuximab or panitumumab with standard therapy or best supportive care including 463 patients with metastatic colorectal tumors with *BRAF* mutations (first-line, second-line, or refractory settings).[721] The addition of an EGFR inhibitor did not improve PFS (HR, 0.88; 95% CI, 0.67–1.14; *P* = .33), OS (HR, 0.91; 95% CI, 0.62–1.34; *P* = .63), or ORR (RR, 1.31; 95% CI, 0.83–2.08, *P* = .25) compared with control arms. Similarly, another meta-analysis identified 7 randomized controlled trials and found that cetuximab and panitumumab did not improve PFS (HR, 0.86; 95% CI, 0.61–1.21) or OS (HR, 0.97; 95% CI, 0.67–1.41) in patients with *BRAF* mutations.[722]

Despite uncertainty over its role as a predictive marker, it is clear that mutations in *BRAF* are a strong prognostic marker.[282,625,711,723-728] A prospective analysis of tissues from patients with stage II and III colon cancer enrolled in the PETACC-3 trial showed that the *BRAF* mutation is prognostic for OS in patients with MSI-L or MSS tumors (HR, 2.2; 95% CI, 1.4–3.4; *P* = .0003).[282] Moreover, an updated analysis of the CRYSTAL trial showed that patients with metastatic colorectal tumors carrying a *BRAF* mutation have a worse prognosis than those with the wild-type gene.[625] Additionally, *BRAF* mutation status predicted OS in the AGITG MAX trial, with an HR of 0.49 (95% CI, 0.33–0.73; *P* = .001).[724] The OS for patients with *BRAF* mutations in the COIN trial was 8.8 months, while those with *KRAS* exon 2 mutations and wild-type *KRAS* exon 2 tumors had OS times of 14.4 months and 20.1 months, respectively.[711] Results from a recent systematic review and meta-analysis of 21 studies, including 9885 patients, suggest that *BRAF* mutation may accompany specific high-risk clinicopathologic characteristics.[729] In particular, an association was observed between *BRAF* mutation and proximal tumor location (OR, 5.22; 95% CI, 3.80–7.17; *P* < .001), T4 tumors (OR, 1.76; 95% CI, 1.16–2.66; *P* = .007), and poor differentiation (OR, 3.82; 95% CI, 2.71–5.36; *P* < .001).

Overall, the panel believes that evidence increasingly suggests that *BRAF* V600E mutation makes response to panitumumab or cetuximab, as single agents or in combination with cytotoxic chemotherapy, highly unlikely. The panel recommends *BRAF* genotyping of tumor tissue (either primary tumor or metastasis[730]) at diagnosis of stage IV disease. Testing for the *BRAF* V600E mutation can be performed on formalin-fixed paraffin-embedded tissues and is usually performed by PCR

amplification and direct DNA sequence analysis. Allele-specific PCR is another acceptable method for detecting this mutation.

HER2 Overexpression

HER2 is a member of the same family of signaling kinase receptors as EGFR and has been successfully targeted in breast cancer in both the advanced and adjuvant settings. HER2 is rarely overexpressed in colorectal cancer (approximately 3% overall), but the prevalence is higher in *RAS/BRAF*–wild type tumors (reported at 5% to 14%).[731,732] Specific molecular diagnostic methods have been proposed for HER2 testing in colorectal cancer,[733] and various therapeutic approaches are being tested in patients with tumors that have HER2 overexpression (eg, trastuzumab plus lapatinib, trastuzumab plus pertuzumab).[731,734] These approaches are currently considered investigational, and enrollment in a clinical trial is encouraged.

Evidence does not support a prognostic role of HER2 overexpression.[735] However, initial results indicate HER2 overexpression may be predictive of resistance to EGFR-targeting monoclonal antibodies.[732,736] For example, in a cohort of 97 patients with *RAS/BRAF*–wild type metastatic colorectal cancer, median PFS on first-line therapy without an EGFR inhibitor was similar regardless of HER2 status.[732] However, in second-line therapy with an EGFR inhibitor, the PFS was significantly shorter in those with HER2 amplification compared with those without HER2 amplification (2.9 months vs. 8.1 months; HR, 5.0; $P < .0001$). Larger confirmatory studies are needed, and the panel does not recommend HER2 testing for prognostication or treatment planning at this time.

Cetuximab with FOLFIRI

Use of cetuximab as initial therapy for metastatic disease was investigated in the CRYSTAL trial, in which patients were randomly assigned to receive FOLFIRI with or without cetuximab.[541] Retrospective analyses of the subset of patients with known *KRAS* exon 2 tumor status showed a statistically significant improvement in median PFS with the addition of cetuximab in the wild-type (9.9 vs. 8.7 months; HR, 0.68; 95% CI, 0.50–0.94; $P = .02$).[541] The statistically significant benefit in PFS for patients with *KRAS* exon 2 wild-type tumors receiving cetuximab was confirmed in a recent publication of an updated analysis of the CRYSTAL data.[625] This recent study included a retrospective analysis of OS in the *KRAS* exon 2 wild-type population and found an improvement with the addition of cetuximab (23.5 vs. 20.0 months, $P = .009$). Importantly, the addition of cetuximab did not affect the quality of life of participants in the CRYSTAL trial.[737] As has been seen with other trials, when DNA samples from the CRYSTAL trial were re-analyzed for additional *KRAS* and *NRAS* mutations, patients with *RAS* wild-type tumors derived a clear OS benefit (HR, 0.69; 95% CI, 0.54–0.88), whereas those with any *RAS* mutation did not (HR, 1.05; 95% CI, 0.86–1.28).[738]

Panitumumab with FOLFIRI

FOLFIRI with panitumumab is listed as an option for first-line therapy in metastatic colorectal cancer based on extrapolation from data in second-line treatment.[535,720,739,740]

Cetuximab with FOLFOX

Three trials have assessed the combination of FOLFOX and cetuximab in first-line treatment of metastatic colorectal cancer. In a retrospective evaluation of the subset of patients with known tumor *KRAS* exon 2 status enrolled in the randomized phase II OPUS trial, addition of cetuximab to FOLFOX was associated with an increased objective response rate (61% vs. 37%; odds ratio, 2.54; $P = .011$) and a very slightly lower risk of disease progression (7.7 vs. 7.2 months [a 15-day difference]; HR, 0.57; 95% CI, 0.36–0.91; $P = .016$) compared with FOLFOX alone in the subset of patients with *KRAS* exon 2 wild-type

tumors.[582] Although data supporting the statistically significant benefits in objective response rate and PFS for patients with tumors characterized by *KRAS* wild-type exon 2 were upheld in an update of this study, no median OS benefit was observed for the addition of cetuximab to chemotherapy (22.8 months in the cetuximab arm vs. 18.5 months in the arm undergoing chemotherapy alone; HR, 0.85; *P* = .39).[741]

Furthermore, in the recent randomized phase III MRC COIN trial, no benefit in OS (17.9 vs. 17.0 months; *P* = .067) or PFS (8.6 months in both groups; *P* = .60) was seen with the addition of cetuximab to FOLFOX or CapeOx as first-line treatment of patients with locally advanced or metastatic colorectal cancer and wild-type *KRAS* exon 2.[711] Exploratory analyses of the COIN trial, however, suggest that there may be a benefit to the addition of cetuximab in patients who received FOLFOX instead of CapeOx.[711] Similarly, a recent pooled analysis of the COIN and OPUS studies found that a benefit was suggested in response rate and PFS with the addition of cetuximab to FOLFOX in patients with *KRAS* exon 2 wild-type tumors, although there was no OS benefit.[742]

Notably, more recent trials examining the efficacity of the addition of cetuximab to oxaliplatin-containing regimens in the first-line treatment of patients with advanced or metastatic colorectal cancer and wild-type *KRAS* exon 2 have not shown any benefit. The addition of cetuximab to the Nordic FLOX regimen showed no benefit in OS or PFS in this population of patients in the randomized phase III NORDIC VII study of the Nordic Colorectal Cancer Biomodulation Group.[743]

However, results from the recent randomized phase III CALGB/SWOG 80405 trial of greater than 3000 patients (discussed in *Cetuximab or Panitumumab vs. Bevacizumab in First-Line*, below) showed that the combination of FOLFOX with cetuximab can be effective in first-line treatment of metastatic colorectal cancer.[583] The panel thus added a recommendation for the use of cetuximab with FOLFOX as initial therapy for patients with advanced or metastatic disease to the 2015 version of these guidelines.

The New EPOC trial, which was stopped early because it met protocol-defined futility criteria, found a lack of benefit to cetuximab with chemotherapy in the perioperative metastatic setting (>85% received FOLFOX or CapeOx; patients with prior oxaliplatin received FOLFIRI).[744] In fact, with less than half of expected events observed, PFS was significantly reduced in the cetuximab arm (14.8 vs. 24.2 months; HR, 1.50; 95% CI, 1.00–2.25; *P* < .048). The panel thus cautions that cetuximab in the perioperative setting may harm patients. The panel therefore does not recommend the use of FOLFOX plus cetuximab in patients with resectable disease and should be used with caution in those with unresectable disease that could potentially be converted to a resectable status.

Panitumumab with FOLFOX

Panitumumab in combination with either FOLFOX[521,695] or FOLFIRI[532] has also been studied in the first-line treatment of patients with metastatic colorectal cancer. Results from the large, open-label, randomized PRIME trial comparing panitumumab plus FOLFOX versus FOLFOX alone in patients with *KRAS/NRAS* wild-type advanced colorectal cancer showed a statistically significant improvement in PFS (HR, 0.72; 95% CI, 0.58–0.90; *P* = .004) and OS (HR, 0.77; 95% CI, 0.64–0.94; *P* = .009) with the addition of panitumumab.[695] Therefore, the combination of FOLFOX and panitumumab remains an option as initial therapy for patients with advanced or metastatic disease. Importantly, the addition of panitumumab had a detrimental impact on PFS for patients with tumors characterized by mutated *KRAS/NRAS* in the

PRIME trial (discussed further in *NRAS and Other KRAS Mutations*, above).[695]

Cetuximab or Panitumumab vs. Bevacizumab in First-Line

The randomized, open-label, multicenter FIRE-3 trial from the German AIO group compared the efficacy of FOLFIRI plus cetuximab to FOLFIRI plus bevacizumab in first-line, *KRAS* exon 2 wild-type, metastatic disease.[709] This trial did not meet its primary endpoint of investigator-read objective response rate in the 592 randomized patients (62.0% vs. 58.0%; *P* = .18). PFS was nearly identical between the arms of the study, but a statistically significant improvement in OS was reported in the cetuximab arm (28.7 vs. 25.0 months; HR, 0.77; 95% CI, 0.62–0.96; *P* = .017). The panel has several criticisms of the trial, including the lack of third-party review and low rates of second-line therapy.[745,746] While the rate of adverse events was similar between the arms, more skin toxicity was observed in those receiving cetuximab.

Results of the phase III CALGB/SWOG 80405 trial, comparing FOLFOX/FOLFIRI with cetuximab or bevacizumab, were recently reported.[583] In this study, patients with wild-type *KRAS* exon 2 received either FOLFOX (73%) or FOLFIRI (27%) and were randomized to receive cetuximab or bevacizumab. The primary endpoint of OS was equivalent between the arms, at 29.0 months (95% CI, 25.7–31.2 months) in the bevacizumab arm versus 29.9 months (95% CI, 27.6–31.2 months) in the cetuximab arm (HR, 0.92; 95% CI, 0.78–1.09; *P* = .34).

Results for the randomized multicenter phase II PEAK trial, which compared FOLFOX/panitumumab with FOLFOX/bevacizumab in first-line treatment of patients with wild-type *KRAS* exon 2, were also published.[747] In the subset of 170 participants with wild-type *KRAS/NRAS* based on extended tumor analysis, PFS was better in the panitumumab arm (13.0 vs. 9.5 months; HR, 0.65; 95% CI, 0.44–0.96; *P* = .03). A trend towards improved OS was seen (41.3 vs. 28.9 months; HR, 0.63; 95% CI, 0.39–1.02; *P* = .06). Although these data are intriguing, definitive conclusions are hindered by the small sample size and limitations of subset analyses.[748]

Economic analyses suggest that bevacizumab may be more cost effective than EGFR inhibitors in first-line therapy for metastatic colorectal cancer.[749,750]

At this time, the panel considers the addition of cetuximab, panitumumab, or bevacizumab to chemotherapy as equivalent choices in the first-line, *RAS* wild-type, metastatic setting.

Therapy After Progression

Decisions regarding therapy after progression of metastatic disease depend on previous therapies. The panel recommends against the use of mitomycin, alfa-interferon, taxanes, methotrexate, pemetrexed, sunitinib, sorafenib, erlotinib, or gemcitabine, either as single agents or in combination, as therapy in patients exhibiting disease progression after treatment with standard therapies. These agents have not been shown to be effective in this setting. Furthermore, no objective responses were observed when single-agent capecitabine was administered in a phase II study of patients with colorectal cancer resistant to 5-FU.[751]

The recommended therapy options after first progression for patients who have received prior 5-FU/LV-based or capecitabine-based therapy are dependent on the initial treatment regimen and are outlined in the guidelines.

Single-agent irinotecan administered after first progression has been shown to significantly improve OS relative to best supportive care [516] or

infusional 5-FU/LV.[752] In the study of Rougier et al,[752] median PFS was 4.2 months for irinotecan versus 2.9 months for 5-FU (*P* = .030), whereas Cunningham et al[516] reported a survival rate at 1 year of 36.2% in the group receiving irinotecan versus 13.8% in the supportive care group (*P* = .0001). Furthermore, no significant differences in OS were observed in the Intergroup N9841 trial when FOLFOX was compared with irinotecan monotherapy after first progression of metastatic colorectal cancer.[753]

A meta-analysis of randomized trials found that the addition of a targeted agent after first-line treatment improves outcomes but also increases toxicity.[754] Another meta-analysis showed an OS and PFS benefit to continuing an anti-angiogenic agent after progression on an anti-angiogenic agent in first-line.[755] Data relating to specific biologic therapies are discussed below.

Cetuximab and Panitumumab in the Non-First-Line Setting
For patients with wild-type *KRAS/NRAS* who experienced progression on therapies *not* containing an EGFR inhibitor, cetuximab or panitumumab plus irinotecan, cetuximab or panitumumab plus FOLFIRI, or single-agent cetuximab or panitumumab[692] is recommended. For patients with wild-type *KRAS/NRAS* progressing on therapies that *did* contain an EGFR inhibitor, administration of an EGFR inhibitor is not recommended in subsequent lines of therapy. No data support switching to either cetuximab or panitumumab after failure of the other drug, and the panel recommends against this practice.

Panitumumab has been studied as a single agent in the setting of metastatic colorectal cancer for patients with disease progression on oxaliplatin/irinotecan-based chemotherapy.[542] In a retrospective analysis of the subset of patients in this trial with known *KRAS* exon 2 tumor status, the benefit of panitumumab versus best supportive care was shown to be enhanced in patients with *KRAS* exon 2 wild-type tumors.[509] PFS was 12.3 weeks versus 7.3 weeks in favor of the panitumumab arm. Response rates to panitumumab were 17% versus 0% in the wild-type and mutant arms, respectively.[509]

Panitumumab has also been studied in combination therapy in the setting of progressing metastatic colorectal cancer. Among patients with *KRAS* exon 2 wild-type tumors enrolled in the large Study 181 comparing FOLFIRI alone versus FOLFIRI plus panitumumab as second-line therapy for metastatic colorectal cancer, addition of the biologic agent was associated with improvement in median PFS (5.9 vs. 3.9 months; HR, 0.73; 95% CI, 0.59–0.90; *P* = .004), although differences in OS between the arms did not reach statistical significance.[535] These results were confirmed in the final results of Study 181.[740] Furthermore, re-analysis of samples from the trial showed that the benefit of the combination was limited to participants with no *RAS* mutations.[756] In addition, secondary analysis from the STEPP trial showed that panitumumab in combination with irinotecan-based chemotherapy in second-line therapy has an acceptable toxicity profile.[739] The randomized multicenter PICCOLO trial, which assessed the safety and efficacy of irinotecan/panitumumab, did not meet its primary endpoint of improved OS in patients with wild-type *KRAS/NRAS* tumors.[720]

Cetuximab has been studied both as a single agent[515,667,689,692] and in combination with irinotecan[515] in patients experiencing disease progression on initial therapy not containing cetuximab or panitumumab for metastatic disease. Results of a large phase III study comparing irinotecan with or without cetuximab did not show a difference in OS, but showed significant improvement in response rate and in median PFS with irinotecan and cetuximab compared with irinotecan alone.[757] Importantly, *KRAS* status was not determined in this study and toxicity

was higher in the cetuximab-containing arm (eg, rash, diarrhea, electrolyte imbalances).[757]

In a retrospective analysis of the subset of patients with known *KRAS* exon 2 tumor status receiving cetuximab monotherapy as second-line therapy,[667] the benefit of cetuximab versus best supportive care was shown to be enhanced in patients with *KRAS* exon 2 wild-type tumors.[692] For those patients, median PFS was 3.7 versus 1.9 months (HR, 0.40; 95% CI, 0.30–0.54; $P < .001$) and median OS was 9.5 versus 4.8 months (HR, 0.55; 95% CI, 0.41–0.74; $P < .001$), in favor of the cetuximab arm.[692]

The recently published randomized, multicenter, open-label, non-inferiority phase 3 ASPECCT trial compared single-agent cetuximab with single-agent panitumumab in the chemotherapy-refractory metastatic setting.[758] The primary non-inferiority OS endpoint was reached, with a median OS of 10.4 months (95% CI, 9.4–11.6) with panitumumab and 10.0 months (95% CI, 9.3–11.0) with cetuximab (HR 0.97; 95% CI, 0.84–1.11). The incidence of adverse events was similar between the groups.

Bevacizumab in the Non-First-Line Setting

In the TML (ML18147) trial, patients with metastatic colorectal cancer who progressed on regimens containing bevacizumab received second-line therapy consisting of a different chemotherapy regimen with or without bevacizumab.[759] This study met its primary endpoint, with patients continuing on bevacizumab having a modest improvement in OS (11.2 months vs. 9.8 months; HR, 0.81; 95% CI, 0.69–0.94; $P = .0062$). Subgroup analyses from this trial found that these treatment effects were independent of *KRAS* exon 2 status.[760]

Similar results were reported from the GONO group's phase III randomized BEBYP trial, in which the PFS of patients who continued on bevacizumab plus a different chemotherapy regimen following progression on bevacizumab was 6.8 months compared to 5.0 months in the control arm (HR, 0.70; 95% CI, 0.52–0.95; $P = .001$).[761] An improvement in OS was also seen in the bevacizumab arm (HR, 0.77; 95% CI, 0.56–1.06; $P = .04$). The EAGLE trial randomized 387 patients with disease progression following oxaliplatin-based therapy with bevacizumab to second-line therapy with FOLFIRI plus either 5 or 10 mg/kg bevacizumab.[762] No difference was seen in PFS or time to treatment failure between the arms, indicating that 5 mg/kg of bevacizumab is an appropriate dose in second-line treatment of metastatic colorectal cancer.

The continuation of bevacizumab following progression on bevacizumab was also studied in a community oncology setting through a retrospective analysis of 573 patients from the US Oncology iKnowMed electronic medical record system.[763] Bevacizumab beyond progression was associated with a longer OS (HR, 0.76; 95% CI, 0.61–0.95) and a longer post-progression OS (HR, 0.74; 95% CI, 0.60–0.93) on multivariate analysis. Analyses of the ARIES observational cohort found similar results, with longer post-progression survival with continuation of bevacizumab (HR, 0.84; 95% CI, 0.73–0.97).[764]

Overall, these data (along with data from the VELOUR trial, discussed below) show that the continuation of VEGF blockade in second-line therapy offers a very modest but statistically significant OS benefit. The panel added the continuation of bevacizumab to the second-line treatment options in the 2013 versions of the NCCN Guidelines for Colon and Rectal Cancers. It may be added to any regimen that does not contain another targeted agent. The panel recognizes the lack of data suggesting a benefit to bevacizumab with irinotecan alone in this

setting, but believes that the option is acceptable, especially in patients whose disease progressed on a 5-FU- or capecitabine-based regimen. When an angiogenic agent is used in second-line therapy, bevacizumab is preferred over ziv-aflibercept and ramucirumab (discussed below), based on toxicity and/or cost.[765]

It may also be appropriate to consider adding bevacizumab to chemotherapy after progression of metastatic disease if it was not used in initial therapy.[523] The randomized phase III ECOG E3200 study in patients who experienced progression through a first-line non-bevacizumab–containing regimen showed that the addition of bevacizumab to second-line FOLFOX modestly improved survival.[523] Median OS was 12.9 months for patients receiving FOLFOX plus bevacizumab compared with 10.8 months for patients treated with FOLFOX alone (P = .0011).[523] Use of single-agent bevacizumab is not recommended because it was shown to have inferior efficacy compared with the FOLFOX alone or FOLFOX plus bevacizumab treatment arms.[523]

Ziv-Aflibercept

Ziv-aflibercept is a recombinant protein that has part of the human VEGF receptors 1 and 2 fused to the Fc portion of human IgG1.[766] It is designed to function as a VEGF trap to prevent activation of VEGF receptors and thus inhibit angiogenesis. The VELOUR trial tested second-line ziv-aflibercept in patients with metastatic colorectal cancer that progressed after one regimen containing oxaliplatin. The trial met its primary endpoint with a small improvement in OS (13.5 months for FOLFIRI/ziv-aflibercept vs. 12.1 months for FOLFIRI/placebo; HR, 0.82; 95% CI, 0.71–0.94; P = .003).[544] A prespecified subgroup analysis from the VELOUR trial found that median OS in the ziv-aflibercept arm versus the placebo arm was 12.5 months (95% CI, 10.8–15.5) versus 11.7 months (95% CI, 9.8–13.8) in patients with prior bevacizumab treatment and 13.9 months (95% CI, 12.7–15.6) versus 12.4 months (95% CI, 11.2–13.5) in patients with no prior bevacizumab treatment.[767]

Adverse events associated with ziv-aflibercept treatment in the VELOUR trial led to discontinuation in 26.6% of patients compared to a 12.1% discontinuation in the placebo group.[544] The most common causes for discontinuation were asthenia/fatigue, infections, diarrhea, hypertension, and venous thromboembolic events.

Ziv-aflibercept has only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients. No data suggest activity of FOLFIRI plus ziv-aflibercept in patients who progressed on FOLFIRI plus bevacizumab or vice-versa, and no data suggest activity of single-agent ziv-aflibercept. Furthermore, the addition of ziv-aflibercept to FOLFIRI in first-line therapy of patients with metastatic colorectal cancer in the phase II AFFIRM study had no benefit and increased toxicity.[768] Thus, the panel added ziv-aflibercept as a second-line treatment option in combination with FOLFIRI or irinotecan only following progression on therapy not containing irinotecan. However, the panel prefers bevacizumab over ziv-aflibercept and ramucirumab (discussed below) in this setting, based on toxicity and/or cost.[765]

Ramucirumab

Another anti-angiogenic agent, ramucirumab, is a human monoclonal antibody that targets the extracellular domain of VEGF receptor 2 to block VEGF signaling.[769] In the multicenter, phase III RAISE trial, 1072 patients with metastatic colorectal cancer whose disease progressed on first-line therapy with fluoropyrimidine/oxaliplatin/bevacizumab were randomized to FOLFIRI with either ramucirumab or placebo.[770] The primary endpoint of OS in the ITT population was met at 13.3 months and 11.7 months in the ramucirumab and placebo groups, respectively, for an HR of 0.84 (95% CI, 0.73–0.98; P = .02). PFS was also improved

with the addition of ramucirumab, at 5.7 months and 4.5 months for the two arms (HR, 0.79; 95% CI, 0.70–0.90; *P* < .0005).

Rates of discontinuation due to adverse events in the RAISE trial were 11.5% in the ramucirumab arm and 4.5% in the placebo arm. The most common grade 3 or worse adverse events were neutropenia, hypertension, diarrhea, and fatigue.

Considering the results of the RAISE trial, the panel added ramucirumab as a second-line treatment option in combination with FOLFIRI or irinotecan following progression on therapy not containing irinotecan. As with ziv-aflibercept, no data suggest activity of FOLFIRI plus ramucirumab in patients who progressed on FOLFIRI plus bevacizumab or vice-versa, and no data suggest activity of single-agent ramucirumab. When an angiogenic agent is used in this setting, the panel prefers bevacizumab over ziv-aflibercept and ramucirumab, because of toxicity and/or cost.[765]

Regorafenib

Regorafenib is a small molecule inhibitor of multiple kinases (including VEGF receptors, fibroblast growth factor [FGF] receptors, platelet-derived growth factor [PDGF] receptors, BRAF, KIT, and RET) that are involved with various processes including tumor growth and angiogenesis.[771] The phase III CORRECT trial randomized 760 patients who progressed on standard therapy to best supportive care with placebo or regorafenib.[527] The trial met its primary endpoint of OS (6.4 months for regorafenib vs. 5.0 months for placebo; HR, 0.77; 95% CI, 0.64–0.94; *P* = .005). PFS was also significantly but modestly improved (1.9 months vs. 1.7 months; HR, 0.49; 95% CI, 0.42–0.58; *P* < .000001).

The randomized, double-blind, phase III CONCUR trial was performed in China, Hong Kong, South Korea, Taiwan, and Vietnam.[772] Patients with progressive metastatic colorectal cancer were randomized 2:1 to receive regorafenib or placebo after 2 or more previous treatment regimens. After a median follow-up of 7.4 months, the primary endpoint of OS was met in the 204 randomized patients (8.8 months in the regorafenib arm vs. 6.3 months in the placebo arm; HR, 0.55; 95% CI, 0.40–0.77; *P* < .001).

Regorafenib has only shown activity in patients who have progressed on all standard therapy. Therefore, the panel added regorafenib as an additional line of therapy for patients with metastatic colorectal cancer refractory to chemotherapy. It can be given before or after trifluridine-tipiracil; no data inform the best order of these therapies.

The most common grade 3 or higher adverse events in the regorafenib arm of the CORRECT trial were hand-foot skin reaction (17%), fatigue (10%), hypertension (7%), diarrhea (7%), and rash/desquamation (6%).[527] Severe and fatal liver toxicity occurred in 0.3% of 1100 patients treated with regorafenib across all trials.[771] In a meta-analysis of 4 studies that included 1078 patients treated with regorafenib for colorectal cancer, gastrointestinal stromal tumor (GIST), renal cell carcinoma, or hepatocellular carcinoma, the overall incidence of all-grade and high-grade hand-foot skin reactions was 60.5% and 20.4%, respectively.[773] In the subset of 500 patients with colorectal cancer, the incidence of all-grade hand-foot skin reaction was 46.6%.

The phase IIIb CONSIGN trial assessed the safety of regorafenib in 2872 patients from 25 countries with refractory metastatic colorectal cancer.[774] The REBECCA study also assessed the safety and efficacy of regorafenib in a cohort of 654 patients with metastatic colorectal cancer within a compassionate use program.[775] The safety profile of

regorafenib in both of these trials was consistent with that seen in the CORRECT trial.

Trifluridine-Tipiracil (TAS-102)

Trifluridine-tipiracil is an oral combination drug, consisting of a cytotoxic thymidine analog, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride, which prevents the degradation of trifluridine. Early clinical studies of the drug in patients with colorectal cancer were promising.[776,777]

Results of the double-blind randomized controlled international phase III RECOURSE trial were published in 2015,[534] followed shortly thereafter by approval of trifluridine-tipiracil by the FDA.[778] With 800 patients with metastatic colorectal cancer who progressed through at least 2 prior regimens randomized 2:1 to receive trifluridine-tipiracil or placebo, the primary endpoint of OS was met (5.3 months vs. 7.1 months; HR, 0.68; 95% CI, 0.58–0.81; $P < .001$).[534] Improvement was also seen in the secondary endpoint of PFS (1.7 months vs. 2.0 months; HR, 0.48; 95% CI, 0.41–0.57; $P < .001$). The most common adverse events associated with trifluridine-tipiracil in RECOURSE were neutropenia (38%), leukopenia (21%), and febrile neutropenia (4%); one drug-related death occurred.[534] A postmarketing surveillance study did not reveal any unexpected safety signals.[779]

The panel added trifluridine-tipiracil as an additional treatment option for patients who have progressed through standard therapies. It can be given before or after regorafenib; no data inform the best order of these therapies. The 144 patients in RECOURSE who had prior exposure to regorafenib obtained similar OS benefit from trifluridine-tipiracil (HR, 0.69; 95% CI, 0.45–1.05) as the 656 patients who did not (HR, 0.69; 95% CI, 0.57–0.83).

Pembrolizumab and Nivolumab

The percentage of stage IV colorectal tumors characterized as MSI-H (mismatch repair-deficient; dMMR) ranged from 3.5% to 5.0% in clinical trials and was 6.5% in the Nurses' Health Study and Health Professionals Follow-up Study.[283,780,781] dMMR tumors contain thousands of mutations, which can encode mutant proteins with the potential to be recognized and targeted by the immune system. However, programmed death-ligands programmed death-ligands 1 and 2 (PD-L1 and PD-L2) on tumor cells can suppress the immune response by binding to programmed cell death protein 1 (PD-1) receptor on T-effector cells. This system evolved to protect the host from an unchecked immune response. Many tumors upregulate PD-L1 and thus evade the immune system.[782] It has therefore been hypothesized that dMMR tumors may be sensitive to PD-1 inhibitors.

Pembrolizumab is a humanized, IgG4 monoclonal antibody that binds to PD-1 with high affinity, preventing its interaction with PD-L1 and PD-L2 and thus allowing immune recognition and response. Pembrolizumab is FDA-approved for the treatment of some patients with unresectable or metastatic melanoma or metastatic non-small cell lung cancer.[783]

A recent phase II study evaluated the activity of pembrolizumab in 11 patients with dMMR colorectal cancer, 21 patients with MMR-proficient colorectal cancer, and 9 patients with dMMR non-colorectal carcinomas.[784] All patients had progressive metastatic disease; the patients in the colorectal arms had progressed through 2 to 4 previous therapies. The primary endpoints were the immune-related objective response rate and the 20-week immune-related PFS rate. The immune-related objective response rates were 40% (95% CI, 12%–74%) in the dMMR colorectal cancer group, 0% (95% CI, 0%–20%) in the MMR-proficient colorectal cancer group, and 71% (95% CI, 29%–96%) in the dMMR non-colorectal group. The 20-week immune-related PFS rates

were 78% (95% CI, 40–97), 11% (95% CI, 1–35), and 67% (95% CI, 22–96), respectively. These results indicate that MSI is a predictive marker for the effectiveness of pembrolizumab across tumor types. Furthermore, the median PFS and OS were not reached in the arm with dMMR colorectal cancer and were 2.2 and 5.0 months, respectively, in the MMR-proficient colorectal cancer group (HR for disease progression or death, 0.10; $P < .001$).

Nivolumab is another humanized IgG4 PD-1 blocking antibody, with FDA indications in melanoma and non-small cell lung cancer.[785] Nivolumab was studied with or without ipilimumab in patients with metastatic colorectal cancer in a phase II trial.[786] The median PFS was 5.3 months (95% CI, 1.4–not estimable) in the MMR-deficient patients who received nivolumab monotherapy, not reached in the MMR-deficient patients who received nivolumab plus ipilimumab, and 1.4 months (95% CI, 1.2–1.9) in the pooled MMR-proficient group.

Based on these data, the panel recommends pembrolizumab or nivolumab as treatment options in patients with metastatic MMR-deficient colorectal cancer in second- or third-line therapy. Patients progressing on either of these drugs should not be offered the other. Additional clinical trials are ongoing to confirm the benefit of these drugs in this setting.

Although PD-1 immune checkpoint inhibitors are generally well tolerated, serious adverse reactions— many immune-mediated—occur in as many as 21% to 41% of patients.[784,786,787] The most common immune-mediated side effects are to the skin, liver, kidneys, gastrointestinal tract, lungs, and endocrine systems.[788-790] Pneumonitis, occurring in approximately 3% to 7% of patients on pembrolizumab or nivolumab, is one of the most serious side effects of PD-1 inhibitors.[788,791-793]

Cetuximab or Panitumumab vs. Bevacizumab in Second-Line

The randomized, multicenter, phase II SPIRITT trial randomized 182 patients with *KRAS* wild-type tumors whose disease progressed on first-line oxaliplatin-based therapy plus bevacizumab to FOLFIRI plus bevacizumab or FOLFIRI plus panitumumab.[794] No difference was seen in the primary endpoint of PFS between the arms (7.7 months in the panitumumab arm vs. 9.2 months in the bevacizumab arm; HR, 1.01; 95% CI, 0.68–1.50; $P = .97$).

Workup and Management of Synchronous Metastatic Disease

The workup for patients in whom metastatic synchronous adenocarcinoma from the large bowel (eg, colorectal liver metastases) is suspected should include a total colonoscopy, CBC, chemistry profile, CEA determination, biopsy if indicated, and CT scan with intravenous contrast of the chest, abdomen, and pelvis.[197] MRI with intravenous contrast should be considered if CT is inadequate. The panel also recommends tumor *KRAS/NRAS* gene status testing at diagnosis of metastatic disease and consideration of *BRAF* genotyping for all patients with *KRAS/NRAS* wild-type metastatic colon cancer (see *The Role of KRAS, NRAS, and BRAF Status*, above).

The panel strongly discourages the routine use of PET/CT scanning for staging, baseline imaging, or routine follow-up. However, the panel recommends consideration of a preoperative PET/CT scan at baseline in selected cases if prior anatomic imaging indicates the presence of potentially surgically curable M1 disease. The purpose of this PET/CT scan is to evaluate for unrecognized metastatic disease that would preclude the possibility of surgical management. A recent randomized clinical trial of patients with resectable metachronous metastases assessed the role of PET/CT in the workup of potential curable disease.[795] While there was no impact of PET/CT on survival, surgical

management was changed in 8% of patients after PET/CT. For example, resection was not undertaken for 2.7% of patients because additional metastatic disease was identified (bone, peritoneum/omentum, abdominal nodes). In addition, 1.5% of patients had more extensive hepatic resections and 3.4% had additional organ surgery. An additional 8.4% of patients in the PET/CT arm had false-positive results, many of which were investigated with biopsies or additional imaging. A meta-analysis of 18 studies including 1059 patients with hepatic colorectal metastases found that PET or PET/CT results changed management in 24% of patients.[796]

Patients with clearly unresectable metastatic disease should not have baseline PET/CT scans. The panel also notes that PET/CT scans should not be used to assess response to chemotherapy, because a PET/CT scan can become transiently negative after chemotherapy (eg, in the presence of necrotic lesions).[797] False-positive PET/CT scan results can occur in the presence of tissue inflammation after surgery or infection.[797] An MRI with intravenous contrast can be considered as part of the preoperative evaluation of patients with potentially surgically resectable M1 liver disease. For example, an MRI with contrast may be of use when the PET and CT scan results are inconsistent with respect to the extent of disease in the liver.

The criterion of potential surgical cure includes patients with metastatic disease that is not initially resectable but for whom a surgical cure may become possible after preoperative chemotherapy. In most cases, however, the presence of extrahepatic disease will preclude the possibility of resection for cure; *conversion to resectability* for the most part refers to a patient with liver-only disease that, because of involvement of critical structures, cannot be resected unless regression is accomplished with chemotherapy (see *Conversion to Resectability*, above).

Close communication among members of the multidisciplinary treatment team is recommended, including an upfront evaluation by a surgeon experienced in the resection of hepatobiliary or lung metastases.

Resectable Synchronous Liver or Lung Metastases

When patients present with colorectal cancer and synchronous liver metastases, resection of the primary tumor and liver can be performed in a simultaneous or staged approach.[798-806] Historically, in the staged approach, the primary tumor was usually resected first. However, the approach of liver resection before resection of the primary followed by adjuvant chemotherapy is now well-accepted.[799,801,807,808] In addition, emerging data suggest that chemotherapy, followed by resection of liver metastases before resection of the primary tumor, might be an effective approach in some patients, although more studies are needed.[809-816]

If a patient with resectable liver or lung metastases is a candidate for surgery, the panel recommends the following options: 1) synchronous or staged colectomy with liver or lung resection[344,352] followed by adjuvant chemotherapy (FOLFOX [preferred], CapeOx [preferred], FLOX, 5-FU/LV, or capecitabine[252,579]); 2) neoadjuvant chemotherapy for 2 to 3 months (ie, FOLFOX [preferred],[343] CapeOx [preferred], or FOLFIRI [category 2B]), followed by synchronous or staged colectomy with liver or lung resection; or 3) colectomy followed by adjuvant chemotherapy (see neoadjuvant options above) and a staged resection of metastatic disease. Overall, combined neoadjuvant and adjuvant treatments should not exceed 6 months.

In the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) remains an option at centers with experience in the surgical and medical oncologic aspects of this procedure.

Unresectable Synchronous Liver or Lung Metastases

For patients with metastatic disease that is deemed to be potentially convertible (see *Conversion to Resectability*, above),[510] chemotherapy regimens with high response rates should be considered, and these patients should be reevaluated for resection after 2 months of preoperative chemotherapy and every 2 months thereafter while undergoing this therapy. If bevacizumab is included as a component of the conversion therapy, an interval of at least 6 weeks between the last dose of bevacizumab and surgery should be applied, with a 6- to 8-week postoperative period before re-initiation of bevacizumab. Patients with disease converted to a resectable state should undergo synchronized or staged resection of colon and metastatic cancer, including treatment with pre- and postoperative chemotherapy for a preferred total perioperative therapy duration of 6 months. Recommended options for adjuvant therapy for these patients include active systemic therapy regimens for advanced or metastatic disease (category 2B for the use of biologic agents in this setting); observation or a shortened course of chemotherapy can also be considered for patients who have completed preoperative chemotherapy. In the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) remains an option at centers with experience in the surgical and medical oncologic aspects of this procedure. Ablative therapy of metastatic disease, either alone or in combination with resection, can also be considered when all measurable metastatic disease can be treated (see *Principles of the Management of Metastatic Disease*).

Patients with disease that is not responding to therapy should receive systemic therapy for advanced or metastatic disease with treatment selection based partly on whether the patient is an appropriate candidate for intensive therapy. Debulking surgery or ablation without curative intent is not recommended.

For patients with liver-only or lung-only disease that is deemed unresectable (see *Determining Resectability*, above), the panel recommends chemotherapy corresponding to initial therapy for metastatic disease (eg, FOLFIRI, FOLFOX, or CapeOx chemotherapy alone or with bevacizumab; FOLFIRI or FOLFOX with panitumumab or cetuximab; FOLFOXIRI alone or with bevacizumab).

Results from one study suggest that there may be some benefit in both OS and PFS from resection of the primary in the setting of unresectable colorectal metastases.[817] Other retrospective analyses also have shown a potential benefit.[818-820] Separate analyses of the SEER database and the National Cancer Data Base also identified a survival benefit of primary tumor resection in this setting.[821,822]

On the other hand, a different analysis of the National Cancer Data Base came to the opposite conclusion.[823] Furthermore, the prospective, multicenter phase II NSABP C-10 trial showed that patients with an asymptomatic primary colon tumor and unresectable metastatic disease who received mFOLFOX6 with bevacizumab experienced an acceptable level of morbidity without upfront resection of the primary tumor.[824] The median OS was 19.9 months. Notably, symptomatic improvement in the primary is often seen with systemic chemotherapy even within the first 1 to 2 weeks. Furthermore, complications from the intact primary lesion are uncommon in these circumstances,[378] and its removal delays initiation of systemic chemotherapy. In fact, a systematic review concluded that resection of the primary does not reduce complications and does not improve OS.[825] However, other systematic reviews and meta-analyses have concluded that, whereas data may not be strong, resection of the primary tumor may provide a survival benefit.[817,826-828] Another systematic review and meta-analysis identified 5 studies that compared open to laparoscopic palliative colectomies in this setting.[829] The laparoscopic approach resulted in

shorter lengths of hospital stays ($P < .001$), fewer postoperative complications ($P = .01$), and lower estimated blood loss ($P < .01$).

Overall, the panel believes that the risks of surgery outweigh the possible benefits of resection of asymptomatic primary tumors in the setting of unresectable colorectal metastases. Routine palliative resection of a synchronous primary lesion should therefore only be considered if the patient has an unequivocal imminent risk of obstruction, acute significant bleeding, perforation, or other significant tumor-related symptoms.

An intact primary is not a contraindication to bevacizumab use. The risk of gastrointestinal perforation in the setting of bevacizumab is not decreased by removal of the primary tumor, because large bowel perforations, in general, and perforation of the primary lesion, in particular, are rare.

Synchronous Abdominal/Peritoneal Metastases

For patients with peritoneal metastases causing obstruction or that may cause imminent obstruction, palliative surgical options include colon resection, diverting colostomy, a bypass of impending obstruction, or stenting, followed by systemic therapy for advanced or metastatic disease.

The primary treatment of patients with nonobstructing metastases is chemotherapy. As mentioned above (see *Cytoreductive Debulking with Hyperthermic Intraperitoneal Chemotherapy*), the panel currently believes that the treatment of disseminated carcinomatosis with complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for selected patients with limited peritoneal metastases for whom R0 resection can be achieved. The panel also recognizes the need for randomized clinical trials that will address the risks and benefits associated with each of these modalities.

Workup and Management of Metachronous Metastatic Disease

On documentation of metachronous, potentially resectable, metastatic disease with dedicated contrast-enhanced CT or MRI, characterization of the disease extent using PET/CT scan should be considered in select cases if a surgical cure of M1 disease is feasible. PET/CT is used at this juncture to promptly characterize the extent of metastatic disease, and to identify possible sites of extrahepatic disease that could preclude surgery.[795,830,831] Specifically, Joyce et al[830] reported that the preoperative PET changed or precluded curative-intent liver resection in 25% of patients. A recent randomized clinical trial assessed the role of PET/CT in the workup of patients with resectable metachronous metastases.[795] While there was no impact of PET/CT on survival, surgical management was changed in 8% of patients after PET/CT. This trial is discussed in more detail in *Workup and Management of Synchronous Metastatic Disease*, above.

As with other conditions in which stage IV disease is diagnosed, a tumor analysis (metastases or original primary) for *KRAS/NRAS* genotype should be performed to define whether anti-EGFR agents can be considered among the potential options. Although *BRAF* genotyping can be considered for patients with tumors characterized by the wild-type *KRAS/NRAS* genes, this testing is currently optional and not a necessary part of deciding whether to use anti-EGFR agents (see *The Role of KRAS, NRAS, and BRAF Status*).

Close communication between members of the multidisciplinary treatment team is recommended, including upfront evaluation by a surgeon experienced in the resection of hepatobiliary and lung metastases. The management of metachronous metastatic disease is

distinguished from that of synchronous disease through also including an evaluation of the chemotherapy history of the patient and through the absence of colectomy.

Patients with resectable disease are classified according to whether they have undergone previous chemotherapy. For patients who have resectable metastatic disease, treatment is resection with 6 months of perioperative chemotherapy (pre- or postoperative or a combination of both), with choice of regimens based on previous therapy. For patients without a history of chemotherapy use, FOLFOX or CapeOx is preferred, with FLOX, capecitabine, and 5-FU/LV as category 2B options. There are also cases when perioperative chemotherapy is not recommended in metachronous disease. In particular, patients with a history of previous chemotherapy and an upfront resection can be observed or may be given an active regimen for advanced disease, and the same is true for patients whose tumors grew on therapy before resection (category 2B for the use of biologic agents in these settings). Observation is preferred if oxaliplatin-based therapy was previously administered. In addition, observation is an appropriate option for patients whose tumors grew through neoadjuvant treatment.

Patients determined to have unresectable disease through cross-sectional imaging scan (including those considered potentially convertible) should receive an active systemic therapy regimen based on prior chemotherapy history (see *Therapy After Progression*, above). In the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) is an option at centers with experience in the surgical and medical oncologic aspects of this procedure. Patients receiving palliative chemotherapy should be monitored with CT or MRI scans approximately every 2 to 3 months.

Endpoints for Advanced Colorectal Cancer Clinical Trials

In the past few years, there has been much debate over what endpoints are most appropriate for clinical trials in advanced colorectal cancer.[832] Quality of life is an outcome that is rarely measured but of unquestioned clinical relevance.[833] While OS is also of clear clinical relevance, it is often not used because large numbers of patients and long follow-up periods are required.[833] PFS is often used as a surrogate, but its correlation with OS is inconsistent at best, especially when subsequent lines of therapy are administered.[833-835] In 2011, The GROUP Español Multidisciplinar en Cancer Digestivo (GEMCAD) proposed particular aspects of clinical trial design to be incorporated into trials that use PFS as an endpoint.[836]

A recent study, in which individual patient data from 3 randomized controlled trials were pooled, tested endpoints that take into account subsequent lines of therapy: duration of disease control, which is the sum of PFS times of each active treatment; and time to failure of strategy, which includes intervals between treatment courses and ends when the planned lines of treatment end (because of death, progression, or administration of a new agent).[834] The authors found a better correlation between these endpoints and OS than between PFS and OS. Another alternative endpoint, time to tumor growth, has also been suggested to predict OS.[837,838] Further evaluation of these and other surrogate endpoints is warranted.

Posttreatment Surveillance

After curative-intent surgery and adjuvant chemotherapy, if administered, post-treatment surveillance of patients with colorectal cancer is performed to evaluate for possible therapeutic complications, discover a recurrence that is potentially resectable for cure, and identify

new metachronous neoplasms at a preinvasive stage. An analysis of data from 20,898 patients enrolled in 18 large, adjuvant, colon cancer, randomized trials showed that 80% of recurrences occurred in the first 3 years after surgical resection of the primary tumor,[262] and a recent study found that 95% of recurrences occurred in the first 5 years.[839]

Surveillance for Locoregional Disease

Advantages of more intensive follow-up of patients with stage II and/or stage III disease have been shown prospectively in several older studies[840-842] and in multiple meta-analyses of randomized controlled trials designed to compare low- and high-intensity programs of surveillance.[843-847] Intensive postoperative surveillance has also been suggested to be of benefit to patients with stage I and IIA disease.[848] Furthermore, a population-based report indicates increased rates of resectability and survival in patients treated for local recurrence and distant metastases of colorectal cancer in more recent years, thereby providing support for more intensive post-treatment follow-up in these patients.[849]

Results from the recent randomized controlled FACS trial of 1202 patients with resected stage I to III disease showed that intensive surveillance imaging or CEA screening resulted in an increased rate of curative-intent surgical treatment compared with a minimum follow-up group that only received testing if symptoms occurred, but no advantage was seen in the CEA and CT combination arm (2.3% in the minimum follow-up group, 6.7% in the CEA group, 8% in the CT group, and 6.6% in the CEA plus CT group).[850] In this study, no mortality benefit to regular monitoring with CEA, CT, or both was observed compared with minimum follow-up (death rate, 18.2% vs. 15.9%; difference, 2.3%; 95% CI, −2.6%–7.1%). The authors concluded that any strategy of surveillance is unlikely to provide a large survival advantage over a symptom-based approach.

The CEAwatch trial compared usual follow-up care to CEA measurements every two months, with imaging performed if CEA increases were seen twice, in 3223 patients at 11 hospitals treated for non-metastatic colorectal cancer in the Netherlands.[851] The intensive CEA surveillance protocol resulted in the detection of more recurrences and recurrences that could be treated with curative intent than usual follow-up, and the time to detection of recurrent disease was shorter. Another randomized trial of 1228 patients found that more intensive surveillance led to earlier detection of recurrences than a less intensive program (less frequent colonoscopy and liver ultrasound and the absence of an annual chest x-ray) but did not affect OS.[852]

The randomized phase III PRODIGE 13 trial will compare 5-year OS after intensive radiological monitoring (abdominal ultrasound, chest/abdomen/pelvis CT, and CEA) with a lower intensity program (abdominal ultrasound and chest x-ray) in patients with resected stage II or III colon or rectal tumors.[853]

Clearly, controversies remain regarding selection of optimal strategies for following up patients after potentially curative colorectal cancer surgery, and the panel's recommendations are based mainly on consensus. The panel endorses surveillance as a means to identify patients who are potentially curable of metastatic disease with surgical resection.

For patients with stage I disease, the panel believes that a less intensive surveillance schedule is appropriate because of the low risk of recurrence and the harms associated with surveillance. Possible harms include radiation exposure with repeated CT scans, psychological

stress associated with surveillance visits and scans, and stress and risks from following up false-positive results. Therefore, for patients with stage I disease, the panel recommends colonoscopy at 1 year. Repeat colonoscopy is recommended at 3 years, and then every 5 years thereafter, unless advanced adenoma (villous polyp, polyp >1 cm, or high-grade dysplasia) is found. In this case, colonoscopy should be repeated in 1 year.[854]

The following panel recommendations for post-treatment surveillance pertain to patients with stage II/III disease who have undergone successful treatment (ie, no known residual disease). History and physical examination should be given every 3 to 6 months for 2 years, and then every 6 months for a total of 5 years. A CEA test (also see *Managing an Increasing CEA Level*, below) is recommended at baseline and every 3 to 6 months for 2 years,[855] then every 6 months for a total of 5 years for patients with stage III disease and those with stage II disease if the clinician determines that the patient is a potential candidate for aggressive curative surgery.[843,855] Colonoscopy is recommended at approximately 1 year after resection (or at 3–6 months postresection if not performed preoperatively because of an obstructing lesion). Repeat colonoscopy is typically recommended at 3 years, and then every 5 years thereafter, unless follow-up colonoscopy indicates advanced adenoma (villous polyp, polyp >1 cm, or high-grade dysplasia), in which case colonoscopy should be repeated in 1 year.[854] More frequent colonoscopies may be indicated in patients who present with colon cancer before 50 years of age. Chest, abdominal, and pelvic CT scan are recommended every 6 to 12 months (category 2B for more frequently than annually) for up to 5 years in patients with stage III disease and those with stage II disease at a high risk for recurrence.[843,856] Routine CEA monitoring and CT scanning are not recommended beyond 5 years. Use of PET/CT to monitor for disease recurrence is not recommended.[856,857] The CT that accompanies a PET/CT is usually a noncontrast CT, and therefore not of ideal quality for routine surveillance.

Surveillance colonoscopies are primarily aimed at identifying and removing metachronous polyps, because data show that patients with a history of colorectal cancer have an increased risk of developing second cancers, particularly in the first 2 years after resection.[854,858] Furthermore, use of post-treatment surveillance colonoscopy has not been shown to improve survival through the early detection of recurrence of the original colorectal cancer.[854] The recommended frequency of post-treatment surveillance colonoscopies is higher (ie, annually) for patients with Lynch syndrome.[27]

CT scan is recommended to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and liver.[843] Hence, CT scan is not routinely recommended in asymptomatic patients who are not candidates for potentially curative resection of liver or lung metastases.[843,856]

The ASCO Clinical Practice Guidelines Committee has endorsed the Follow-up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer from Cancer Care Ontario (CCO).[859,860] These guidelines differ only slightly from the surveillance recommendations in these NCCN Guidelines for Colon Cancer. While ASCO/CCO recommend abdominal and chest CT annually for 3 years in patients with stage II and III disease, the NCCN Panel recommends semi-annual to annual scans for 5 years (category 2B for more frequent than annual scanning). The panel bases its recommendation on the fact that approximately 10% of patients will recur after 3 years.[262,839] The American Society of Colon and Rectal Surgeons also released surveillance guidelines, which are also very similar to NCCN

surveillance recommendations.[861] One exception is the inclusion of intensive surveillance for patients with resected stage I colon or rectal cancer if the provider deems the patient to be at increased risk for recurrence.

Surveillance for Metastatic Disease

Patients who had resection of metastatic colorectal cancer can undergo subsequent curative-intent resection of recurrent disease (*see Surgical Management of Colorectal Metastases*, above). A retrospective analysis of 952 patients who underwent resection at Memorial Sloan Kettering Cancer Center showed that 27% of patients with recurrent disease underwent curative-intent resection and that 25% of those patients (6% of recurrences; 4% of the initial population) were free of disease for ≥36 months.[862]

Panel recommendations for surveillance of patients with stage IV colorectal cancer with NED after curative-intent surgery and subsequent adjuvant treatment are similar to those listed for patients with stage II/III disease, except that certain evaluations are performed more frequently. Specifically, the panel recommends that these patients undergo contrast-enhanced CT scan of the chest, abdomen, and pelvis every 3 to 6 months in the first 2 years after adjuvant treatment (category 2B for frequency <6 months) and then every 6 to 12 months for up to a total of 5 years. CEA testing is recommended every 3 to 6 months for the first 2 years and then every 6 months for a total of 5 years, as in early-stage disease. Again, use of PET/CT scans for surveillance is not recommended. A recent analysis of patients with resected or ablated colorectal liver metastases found that the frequency of surveillance imaging did not correlate with time to second procedure or median survival duration.[863] Those scanned once per year survived a median of 54 months versus 43 months for those scanned 3 to 4 times per year (*P* = .08), suggesting that annual scans may be sufficient in this population.

Managing an Increasing CEA Level

Managing patients with an elevated CEA level after resection should include colonoscopy; chest, abdominal, and pelvic CT scans; physical examination; and consideration of PET/CT scan. If imaging study results are normal in the face of a rising CEA, repeat CT scans are recommended every 3 months until either disease is identified or CEA level stabilizes or declines.

In a recent retrospective chart review at Memorial Sloan Kettering Cancer Center, approximately half of elevations in CEA levels after R0 resection of locoregional colorectal cancer were false positives, with most being single high readings or repeat readings in the range of 5 to 15 ng/mL.[864] In this study, false-positive results greater than 15 ng/mL were rare, and all results greater than 35 ng/mL represented true positives. Following a systematic review and meta-analysis, the pooled sensitivity and specificity of CEA at a cut-off of 10 ng/mL were calculated at 68% (95% CI, 53%–79%) and 97% (95% CI, 90%–99%), respectively.[865,866] In the first 2 years post-resection, a CEA cut-off of 10 ng/mL is estimated to detect 20 recurrences, miss 10 recurrences, and result in 29 false positives.

Panel opinion was divided on the usefulness of PET/CT scan in the scenario of an elevated CEA with negative, good-quality CT scans (ie, some panel members favored use of PET/CT in this scenario whereas others noted that the likelihood of PET/CT identifying surgically curable disease in the setting of negative good-quality CT scans is vanishingly small). A recent systematic review and meta-analysis found 11 studies (510 patients) that addressed the use of PET/CT in this setting.[867] The pooled estimates of sensitivity and specificity for the detection of tumor

recurrence were 94.1% (95% CI, 89.4–97.1%) and 77.2% (95% CI, 66.4–85.9), respectively. Use of PET/CT scans in this scenario is permissible within these guidelines. The panel does not recommend a so-called blind or CEA-directed laparotomy or laparoscopy for patients whose workup for an increased CEA level is negative,[868] nor does it recommend use of anti-CEA-radiolabeled scintigraphy.

Survivorship

The panel recommends that a prescription for survivorship and transfer of care to the primary care physician be written.[869] The oncologist and primary care provider should have defined roles in the surveillance period, with roles communicated to patient. The care plan should include an overall summary of treatments received, including surgeries, radiation treatments, and chemotherapy. The possible expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment should be described. Finally, surveillance and health behavior recommendations should be part of the care plan.

Disease-preventive measures, such as immunizations; early disease detection through periodic screening for second primary cancers (eg, breast, cervical, or prostate cancers); and routine good medical care and monitoring are recommended (see the NCCN Guidelines for Survivorship, available at www.NCCN.org). Additional health monitoring should be performed as indicated under the care of a primary care physician. Survivors are encouraged to maintain a therapeutic relationship with a primary care physician throughout their lifetime.[870]

Other recommendations include monitoring for late sequelae of colon cancer or the treatment of colon cancer, such as chronic diarrhea or incontinence (eg, patients with stoma).[871-876] Other long-term problems common to colorectal cancer survivors include oxaliplatin-induced peripheral neuropathy, fatigue, insomnia, cognitive dysfunction, body image issues (especially as related to an ostomy), and emotional or social distress.[877-883] Specific management interventions to address these and other side effects are described in a review,[884] and a survivorship care plan for patients with colorectal cancer have been published.[885]

The NCCN Guidelines for Survivorship, available at www.NCCN.org, provide screening, evaluation, and treatment recommendations for common consequences of cancer and cancer treatment to aid health care professionals who work with survivors of adult-onset cancer in the post-treatment period, including those in specialty cancer survivor clinics and primary care practices. The NCCN Guidelines for Survivorship include many topics with potential relevance to survivors of colorectal cancer, including Anxiety, Depression, and Distress; Cognitive Dysfunction; Fatigue; Pain; Sexual Dysfunction; Healthy Lifestyles; and Immunizations. Concerns related to employment, insurance, and disability are also discussed. The American Cancer Society has also established guidelines for the care of survivors of colorectal cancer, including surveillance for recurrence, screening for subsequent primary malignancies, the management of physical and psychosocial effects of cancer and its treatment, and promotion of healthy lifestyles.[870]

Healthy Lifestyles for Survivors of Colorectal Cancer

Evidence also indicates that certain lifestyle characteristics, such as smoking cessation, maintaining a healthy BMI, engaging in regular exercise, and making certain dietary choices are associated with improved outcomes and quality of life after treatment for colon cancer.

In a prospective observational study of patients with stage III colon cancer enrolled in the CALGB 89803 adjuvant chemotherapy trial, DFS

was found to be directly related to the amount of exercise in which the patients engaged.[886] In addition, a study of a large cohort of men treated for stage I through III colorectal cancer showed an association between increased physical activity and lower rates of colorectal cancer-specific mortality and overall mortality.[887] More recent data support the conclusion that physical activity improves outcomes. In a cohort of more than 2000 survivors of non-metastatic colorectal cancer, those who spent more time in recreational activity had a lower mortality than those who spent more leisure time sitting.[888] In addition, recent evidence suggests that both pre- and post-diagnosis physical activity decreases colorectal cancer mortality. Women enrolled in the Women's Health Initiative study who subsequently developed colorectal cancer had lower colorectal cancer-specific mortality (HR, 0.68; 95% CI, 0.41–1.13) and all-cause mortality (HR, 0.63; 95% CI, 0.42–0.96) if they reported high levels of physical activity.[889] Similar results were seen in other studies and in recent meta-analyses of prospective studies.[890-893]

A retrospective study of patients with stage II and III colon cancer enrolled in NSABP trials from 1989 to 1994 showed that patients with a BMI of 35 kg/m^2 or greater had an increased risk of disease recurrence and death.[894] Data from the ACCENT database also found that pre-diagnosis BMI has a prognostic impact on outcomes in patients with stage II/III colorectal cancer undergoing adjuvant therapy.[895] An analysis of participants in the Cancer Prevention Study-II Nutrition Cohort who subsequently developed non-metastatic colorectal cancer found that pre-diagnosis obesity but not post-diagnosis obesity was associated with higher all-cause and colorectal cancer-specific mortality.[896] A meta-analysis of prospective cohort studies found that pre-diagnosis obesity was associated with increased colorectal cancer-specific and all-cause mortality.[897] Other analyses confirm the increased risk for recurrence and death in obese patients.[71,898-901]

In contrast, pooled data from first-line clinical trials in the ARCAD database indicate that a low BMI may be associated with an increased risk of progression and death in the metastatic setting, whereas a high BMI may not be.[902] In addition, results of one retrospective observational study of a cohort of 3408 patients with resected stage I to III colorectal cancer suggest that the relationship between mortality and BMI might be U shaped, with the lowest mortality for those with BMI 28 kg/m^2.[903] However, several possible explanations for this so-called "obesity paradox" have been suggested.[904] Overall, the panel believes that survivors of colorectal cancer should be encouraged to achieve and maintain a healthy body weight (see the NCCN Guidelines for Survivorship at www.NCCN.org).

A diet consisting of more fruits, vegetables, poultry, and fish; less red meat; more whole grains; and fewer refined grains and concentrated sweets has been found to be associated with an improved outcome in terms of cancer recurrence or death.[905] There is also some evidence that higher postdiagnosis intake of total milk and calcium may be associated with a lower risk of death in patients with stage I, II, or III colorectal cancer.[77] Recent analysis of the CALGB 89803 trial found that higher dietary glycemic load was also associated with an increased risk of recurrence and mortality in patients with stage III disease.[906] Another analysis of the data from CALGB 89803 found an association between high intake of sugar-sweetened beverages and an increased risk of recurrence and death in patients with stage III colon cancer.[907] The link between red and processed meats and mortality in survivors of non-metastatic colorectal cancer has been further supported by recent data from the Cancer Prevention Study II Nutrition Cohort, in which survivors with consistently high intake had a higher risk of colorectal cancer-specific mortality than those with low intake (RR, 1.79; 95% CI, 1.11–2.89).[69]

A discussion of lifestyle characteristics that may be associated with a decreased risk of colon cancer recurrence, such as those recommended by the American Cancer Society,[908] also provides "a teachable moment" for the promotion of overall health, and an opportunity to encourage patients to make choices and changes compatible with a healthy lifestyle. In addition, a recent trial showed that telephone-based health behavior coaching had a positive effect on physical activity, diet, and BMI in survivors of colorectal cancer, suggesting that survivors may be open to health behavior change.[909]

Therefore, survivors of colorectal cancer should be encouraged to maintain a healthy body weight throughout life; adopt a physically active lifestyle (at least 30 minutes of moderate intensity activity on most days of the week); consume a healthy diet with emphasis on plant sources; limit alcohol consumption; and quit smoking.[908] Activity recommendations may require modification based on treatment sequelae (ie, ostomy, neuropathy), and diet recommendations may be modified based on the severity of bowel dysfunction.[910]

Secondary Chemoprevention for Colorectal Cancer Survivors

Limited data suggest a link between post-colorectal-cancer-diagnosis statin use and increased survival.[90,911,912] A meta-analysis that included 4 studies found that post-diagnosis statin use increased OS (HR, 0.76; 95% CI, 0.68–0.85; $P < .001$) and cancer-specific survival (HR, 0.70; 95% CI, 0.60–0.81; $P < .001$).[911]

Abundant data show that low-dose aspirin therapy after a diagnosis of colorectal cancer decreases the risk of recurrence and death.[913-919] For example, a population-based, observational, retrospective cohort study of 23,162 patients with colorectal cancer in Norway found that post-diagnosis aspirin use was associated with improved colorectal cancer-specific survival (HR, 0.85; 95% CI, 0.79–0.92) and OS (HR, 0.95; 95% CI, 0.90–1.01).[913] Some evidence suggests that tumor mutations in *PIK3CA* may be predictive for response to aspirin, although the data are somewhat inconsistent and other predictive markers have also been suggested.[915,920-924]

Based on these data, the panel believes that survivors of colorectal cancer can consider taking low-dose aspirin to reduce their risk of recurrence and death. Importantly, aspirin may increase the risk of gastrointestinal bleeding and hemorrhagic stroke, and these risks should be discussed with colorectal cancer survivors.[925]

Summary

The panel believes that a multidisciplinary approach is necessary for managing colorectal cancer. The panel endorses the concept that treating patients in a clinical trial has priority over standard or accepted therapy.

The recommended surgical procedure for resectable colon cancer is an en bloc resection and adequate lymphadenectomy. Adequate pathologic assessment of the resected lymph nodes is important with a goal of evaluating at least 12 nodes. Adjuvant therapy with FOLFOX or CapeOx (both category 1, preferred), FLOX (category 1), 5-FU/LV (category 2A), or capecitabine (category 2A) is recommended by the panel for patients with stage III disease. Adjuvant therapy for patients with high-risk stage II disease is also an option; the panel recommends 5-FU/LV with or without oxaliplatin (FOLFOX or FLOX) or capecitabine with or without oxaliplatin (category 2A for all treatment options). Patients with resectable T4b tumors may be treated with neoadjuvant systemic therapy prior to colectomy.

Patients with metastatic disease in the liver or lung should be considered for surgical resection if they are candidates for surgery and

if all original sites of disease are amenable to resection (R0) and/or ablation. Six months of perioperative systemic therapy should be administered to patients with synchronous or metachronous resectable metastatic disease. When a response to chemotherapy would likely convert a patient from an unresectable to a resectable state (ie, conversion therapy), this therapy should be initiated.

The recommended post-treatment surveillance program for patients with resected disease includes serial CEA determinations, and periodic chest, abdominal, and pelvic CT scans; colonoscopic evaluations; and a survivorship plan to manage long-term side effects of treatment, facilitate disease prevention, and promote a healthy lifestyle.

Recommendations for patients with disseminated metastatic disease represent a continuum of care in which lines of treatment are blurred rather than discrete. Principles to consider at initiation of therapy include pre-planned strategies for altering therapy for patients in both the presence and absence of disease progression, including plans for adjusting therapy for patients who experience certain toxicities. Recommended initial therapy options for advanced or metastatic disease depend on whether the patient is appropriate for intensive therapy. The more intensive initial therapy options include FOLFOX, FOLFIRI, CapeOx, and FOLFOXIRI. Addition of a biologic agent (eg, bevacizumab, cetuximab, panitumumab) is an option in combination with some of these regimens, depending on available data. Systemic therapy options for patients with progressive disease depend on the choice of initial therapy.

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